REMARKS

A check for $860 for the fees for a three-month extension of time ($475) and for filing of an RCE ($385) and a DECLARATION regarding material inserted in the specification accompany this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050.

Claims 1-8, 11, 13-20, 44-53, 69-71 and 75 are pending in the application. Claim 12 is cancelled herein without prejudice or disclaimer. Claims 11, 13-15, 44 and 75 are amended herein to more particularly point out and distinctly claim the subject matter.

The specification is amended herein to incorporate material at page 70 of the instant specification from U.S. Provisional Application Serial No. 60/240,335, pages 48-49, that had been incorporated by reference in its entirety in the instant application (see page 1). A Declaration, executed by Applicant's representative, stating that the amendatory material is the material incorporated by reference is provided. The specification is also amended to correct minor typographical errors. No new matter is added.

Claims 11, 13 and 14 are amended to more distinctly claim the subject matter by deleting the recitation "of an AKAP10 allele." Claims 13 and 14 are further amended to include the recitation —or the complement thereof—, basis for which is found in claim 11, from which they depend. Claims 13, 14 and 75 are also amended to more particularly point out and distinctly claim the subject matter by including the recitation —a free hydroxyl for enzymatic extension—, basis for which can be found throughout the specification (for example, see page 61, lines 1-12; page 57, lines 13-16; and page 46, line 8 through page 47, line 17). By definition, a primer is a short oligonucleotide that provides a free hydroxyl for DNA or RNA synthesis by the appropriate polymerase enzyme (see Patel *et al.*, *The GeneEd Glossary* (1998), page 87; and Lewin, *Genes* (1983), page 680).

Claim 15 is amended to delete redundant matter recited in the parent claim. Claim 44 is amended to more distinctly claim the subject matter by

reciting that the variant protein includes a polymorphism that results in a valine at a position corresponding to amino acid residue 646 of SEQ ID NO:4, basis for which is found throughout the specification (for example, see page 5, lines 2-8). Claim 44 is also amended to correct a minor typographical error. Claim 55 is amended to more distinctly claim the subject matter by reciting that the expressed protein is encoded by the vector, basis for which is found throughout the specification (for example, see page 78, line 18 through page 79, line 28). Claim 75 is amended to more distinctly claim the subject matter by including the recitation –wherein the primer has a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to a position selected from the group consisting of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18–, basis for which is found throughout the specification (for example, see page 17, line 24 through page 18, line 3). These amendments do not alter the scope or content of the claims, but are designed to more particularly point out and distinctly claim the subject matter encompassed by the claims. No new matter has been added. Accordingly, entry of the amendments to the claims is respectfully requested.

REJECTION OF CLAIMS 1-8, 11-20, 44-53, 69-71 AND 75 UNDER 35 U.S.C. §101

Claims 1-8, 11-20, 44-53, 69-71 and 75 are rejected under 35 U.S.C. §101 because the claimed subject matter allegedly is not supported by either a substantial asserted utility or a well established utility. This rejection is respectfully traversed.

RELEVANT LAW

An applicant need only make one credible assertion of specific utility to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not "credible," do not render a claimed invention lacking in utility. See, *e.g.*, *Raytheon v. Roper*, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984) ("When a properly claimed invention

meets at least one stated objective, utility under 35 U.S.C. 101 is clearly shown."); *In re Gottlieb*, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); *In re Malachowski*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988).

The MPEP provides further guidance to its office personnel that:

> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. See, *e.g.*, *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). **Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.**

Further, the MPEP at 2107.02(III)(A) states:

> In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101. See., *e.g.*, *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 122 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).
>
> Compliance with 35 U.S.C. 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 835 (1984). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that is it more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness or argument."); *In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985). A preponderance of the

> evidence exists when it suggests that it is more likely than not that the assertion in question is true. *Herman v. Huddleston*, 459 U.S. 375, 390 (1983). To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art. Of course, a person of ordinary skill must have the benefit of both facts and reasoning in order to asses the truth of a statement. This means that if the applicant has presented facts that support the reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). The initial evidentiary standard used during evaluation of this question is preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false).

MPEP §2107 II(B)(1)(ii) states that:

> An applicant need only provide **one credible assertion of specific and substantial utility for each claimed invention** to satisfy the utility requirement.

In addition, MPEP §2107 II.(A)(3), states that:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Rejections under 35 U.S.C. §101 rarely have been sustained by federal courts. Generally, in these rare cases, the 35 U.S.C. §101 rejection was sustained either because the applicant failed to disclose any utility or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

ANALYSIS

As set forth above, an applicant need only provide **one credible assertion of specific and substantial utility** to satisfy the utility requirement. It is respectfully submitted that the instant patent specification asserts several useful applications of the claimed allelic variants of the AKAP10 gene and gene products, in addition to methods, kits and solid supports that have useful properties or applications.

In setting forth this rejection, the Examiner relies on *Brenner v. Manson*, 148 USPQ 689. *Brenner* holds that no patent may issue for a chemical compound or a process for making such compound unless the compound is shown to have some practical utility (*i.e.*, does not require further experimentation to find a use for it or to put it into a form such that it is useful). In instances in which such utility is lacking, the claimed products or methods lack utility because the claimed methods are used to synthesize compounds that have no known utility and the compound has no known use. Thus it appears that the Examiner is alleging that the claims at issue are drawn to methods of making compounds or to compounds that have no known use, and that further experimentation must be done to ascertain uses for the compounds.

Applicant respectfully disagrees and submits that no further research is required to identify or reasonably confirm a "real world" context of use for the claimed subject matter. The application provides a number of useful properties or applications. For example, the application shows the use of the AKAP10-5 and AKAP10-1 alleles as markers for predicting susceptibility to morbidity and/or increased or early mortality (page 5, lines 25-26) and the use of polymorphic AKAP genes as markers for detecting predisposition to disease and various conditions (page 69, lines 26-40). In this application, the application discloses that the frequency of AKAP allelic variants decreases with age. In other words, the AKAP allelic variant does not appear at a high frequency in elderly people. This decreasing occurrence of the allelic variants in the elderly indicates that those with the AKAP allelic variant are susceptible to early mortality, and thus these allelic variants are potential morbidity susceptibility genes, or genes associated with increased early mortality.

Furthermore, there is data in the application demonstrating association of AKAP allelic variants with a phenotype. U.S. Provisional Application Serial No. 60/240,335, to which the instant application claims priority, and which is incorporated by reference in its entirety (see instant specification page 1, lines 26-28), discloses at page 48, lines 15-25 that:

> The healthy database was then stratified (*i.e.*, sorted) by information given by the donors about common disorders from which their parents suffered (the donor's familial history of disease). The study found that, in males 50 years and older, the AKAP10-5 allele is associated with cardiovascular disease. The subpopulation of donors 50 years and older was used in the study to ensure that the parents were old enough to have potentially manifested the disease.
>
> The frequency of the heterozygous genotype (A/G; ILE/VAL) showed an increase between none affected, one affected and both affected groups. For a disease that showed no correlation, there was no difference among these groups.

Thus, the specification describes a correlation between the presence of the AKAP10-5 allele and cardiovascular disease in males 50 years and older. Using as a baseline the frequency of the heterozygous genotype observed when neither parent was affected by the disease, the frequency of the heterozygous genotype increases in groups where one parent was affected by the disease, and increases further in groups where both parents were affected. For a disease that shows no correlation to the presence of the AKAP10-5 allele, there was no difference among these groups.

U.S. Provisional Application Serial No. 60/240,335 also discloses, at page 48, line 28 through page 49, line 13, that:

> The frequency of the AKAP10-5 SNP in DNA samples isolated from the blood of patients diagnosed with either coronary artery disease (CAD) or abnormal left ventricular (LV) function was investigated. These disorders were diagnosed in the patient population by cardiac catheterization. The left ventricle is the most important of the four chambers in the heart because it generates the pressure needed to circulate blood throughout the body. In addition, poor function of the left ventricle can be the indirect cause of other problems such as certain abnormal heart rhythms and stroke.

> The AKAP allele frequencies in the initial set of patient DNAs (145 patients), broken out by 3 clinical descriptors {ethnic group (white, hispanic or black), coronary artery disease (yes or no), and left ventricular function (normal or abnormal, as measured by reduced LV ejection fraction)} were calculated.
>
> The results showed that the G allele appears to be more frequent in blacks > whites > hispanics, and more frequent in patients with abnormal LV function (a strong predictor of cardiovascular mortality).

Hence, the specification also shows that the G allele appears to be more frequent in Blacks > Whites > Hispanics. This correlates with the death rate statistics for stroke and coronary heart disease from the Centers for Disease Control (see supporting documents), which showed that death rates from these cardiovascular diseases for Black non-Hispanics is higher than it is for White non-Hispanics, which is higher than it is for Hispanics.

The disclosure of U.S. Provisional Application Serial No. 60/240,335, which is incorporated by reference into the instant specification, also shows that the AKAP10-5 SNP occurs more frequently in patients with abnormal left ventricular function. Because poor function of the left ventricle can be the indirect cause of other problems such as certain abnormal heart rhythms and stroke, the AKAP10 allelic variants can serve as markers for morbidity susceptibility, or as markers for increased early mortality.

A "real world" use for AKAP10 allelic variants described in the application is as diagnostic and prognostic aids in the selection of drug therapies or treatment regimens in patients with a familial history of diseases associated with changes in frequency distribution of AKAP10 allelic variants. These diseases include diseases such as cardiovascular disease or abnormal left ventricular function. Because, as described in the application, the occurrence of these allelic variants is correlated with early death and with facilitating disease-specific susceptibility, individuals with alleles correlated with such early death are candidates for implementing a more aggressive treatment regime at disease onset, or counseling and implementing of appropriate lifestyle changes prior to disease manifestation. Hence, AKAP10 allelic variants are useful as markers for

predicting susceptibility to morbidity and/or increased or early mortality and as markers for detecting predisposition to disease and various conditions. Such a use provides a public benefit, and thus is a substantial utility under 35 U.S.C. §101.

The application describes a variety of methods to detect the presence of AKAP10 allelic variants. These methods include immunological assays and genetic assays. An isolated recombinant, synthetic, or native polynucleotide is an immunogen (antigen) for the production of monoclonal or polyclonal antibodies specifically reactive with AKAP proteins (page 84, lines 25-28). Thus, the isolated nucleic acid molecules of claims 1-8 can be used to produce polypeptides for the production of monoclonal or polyclonal antibodies that can be used in diagnostic or prognostic assays to detect the presence of AKAP10 allelic variants in patients. Alternatively, such molecules have use in nucleic-acid based assays, such as mass spectrometric assays (i.e. PROBE) described in the application.

Claims 11-18, 47-50, 69-71 and 75 are directed to primers, probes, antisense nucleic acid molecules, kits, solid supports, microarrays and isolated nucleic acids. It is respectfully submitted that the subject matter of these claims is useful in methods of detecting the presence of AKAP10 allelic variants in a subject. As discussed above, the presence of an AKAP10 allelic variant is useful, for example, as a marker for detecting predisposition to disease.

The specification discloses a number of methods of detecting the presence of AKAP10 allelic variant, including methods using sequence-specific polynucleotides, oligonucleotides, probes and primers such as nucleic acid hybridization of sequence-specific probes, nucleic acid sequencing, selective amplification, cleavage of mismatched heteroduplexes of nucleic acid and probe, alterations of electrophoretic mobility, primer specific extension, oligonucleotide ligation assay and single-stranded conformation polymorphism analysis (page 46, lines 18-27). One asserted utility of the subject matter of claims 11-18, 47-50, 69-71 and 75 is use in assays analyzing nucleic acid that encodes an AKAP10 allelic variant. Thus, it is respectfully submitted that the subject matter of claims 11-18, 47-50, 69-71 and 75 is useful for analyzing nucleic acid encoding an

AKAP10 allelic variant. The MPEP clearly acknowledges that screening assays that are useful in analyzing compounds "have a clear, specific and unquestionable utility" (see MPEP §2107.01(I)).

Claims 19, 20 and 44-46 are directed to incorporating the claimed isolated nucleic acid molecules encoding polymorphic human AKAP10 proteins into vectors to introduce heterologous DNA into cells for either expression or replication thereof or for further manipulation. Such vectors and cells are useful for the production of the polymorphic proteins encoded by the isolated nucleic acid molecules, and for the preparation of synthetic or recombinant polymorphic human AKAP10 proteins and fragments thereof that are substantially free of contamination from other AKAPs and proteins, the presence of which can interfere with analysis of the polymorphic proteins (page 79, lines 21-30). These AKAP allelic variant gene products are useful as pharmaceutical targets and gene therapy targets, such as in defects in protein phosphorylation, AKAP-directed subcellular localization of cAMP-dependent protein kinase or G-protein mediated receptor-signalling pathways (page 69, lines 14-30). Thus, the claimed vectors, cells and methods are useful for the production of AKAP10 variant protein for use in screening assays, such as screening assays to identify patients having such a mutation, which allows for the selection of a specific treatment regime (for example, see page 89, lines 10-19). Accordingly, it is respectfully submitted that the subject matter of claims 19, 20, 44-46 and 51-53 is useful for producing AKAP10 variant protein for use in screening assays.

Therefore, Applicant respectfully submits that at least one credible assertion of specific utility is set forth for all of the claimed subject matter, thereby satisfying the requirements of 35 U.S.C. §101 and 35 U.S.C. §112. Reconsideration and withdrawal of this rejection as applied to claims 1-8, 11-20, 44-53, 69-71 and 75 is therefore respectfully requested.

REBUTTAL TO EXAMINER'S ARGUMENTS

Screening Assay Allegedly Does Not Provide a Specific Benefit

The Examiner alleges that the asserted utility of the claimed polynucleotides as a component of a screening assay does not satisfy the utility requirement of §101 because such a use does not provide a specific benefit in currently available form. The Examiner contends:

> In effect, applicant's position is that the claimed polynucleotides are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean.

Applicant respectfully disagrees. In setting forth this rejection, which relies on *Brenner v. Manson*, 148 USPQ 689, it appears that the Examiner is referring to instances in which the claims at issue are drawn to methods of making compounds or to compounds that have no known use so that further experimentation must be done to ascertain uses for the compounds. *Brenner* holds that no patent may issue for a chemical compound or a process for making such compound unless the compound is shown to have some practical utility (*i.e.*, does not require further experimentation to find a use for it or to put it into a form such that it is useful). In instances in which such utility is lacking, the claimed products or methods lack utility because the claimed methods are used to synthesize compounds that have no known utility and the compound has no known use.

The Examiner, thus, is confusing instances in which experiments or research must be done in order to ascertain a use for a product or process with instances in which a product or process is claimed that is used by a researcher conducting research. In the first instance, patentable utility may be lacking; in the second, however, practical and patentable utility is not lacking. Many compounds and processes are intended for use in research and possess patentable utility. Reagents, such as Tris buffer, and apparatus, such as gel electrophoresis devices, have uses that are most likely only experimental in the sense that they are used by researchers conducting experiments. Clearly, buffers and electrophoresis devices are patentable subject matter. Similarly, merely

because the instantly claimed polynucleotides may be used by those who are engaged in research does not render them unpatentable for lack of utility. Their use is in definite and presently available form.

Brenner is not applicable to the instantly claimed products, which are not compounds of unknown utility, but are products that have a use. Further research is not required to use the claimed products; their use is definite and is in currently available form. The specification exemplifies the use of the primers, probes and antisense nucleic acid molecules in assays that detect the presence of AKAP10 variants by specifically hybridizing adjacent to or at a polymorphic region of an AKAP10 allelic variant or the complement thereof (for example, see pages 46-68). Such use is not experimental, but is definite and presently available and is of practical value, since identifying the presence of an AKAP10 allelic variant in a patient with a familial history of diseases associated with changes in frequency distribution of AKAP10 allelic variants allows for devising appropriate therapies prior to disease manifestation. Similarly, *Brenner* is inapplicable to the claimed methods.

Regarding the utility of screening assays as research tools, MPEP §2107.01(I). states:

> **Research Tools**
>
> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, **screening assays**, and nucleotide sequencing techniques **have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.**

There is a difference between a use of a compound in research and experiments and instances in which experimentation must be done to establish a use. The

latter may be an "experimental" use; the former use, however, is an acceptable practical utility. The MPEP clearly acknowledges that screening assays that are useful in analyzing compounds **"have a clear, specific and unquestionable utility."**

Alleged Lack of Statistical Significance

In setting forth this rejection, the Examiner admits that the specification asserts that the claimed nucleic acid is useful as a marker for increased or early susceptibility to morbidity, but alleges that the data presented in Example 4 does not support the conclusion that the AKAP10-5 G allele is associated with increased susceptibility to morbidity, increased or early mortality or morbidity and increased or early mortality as compared to the susceptibility of a subject who does not comprise the allelic variant. The Examiner alleges that "the minimal difference of 4.1% between young and old populations would require the researcher to further analyze the information to determine whether the polymorphism was meaningful" and from the Examiner's statistical calculations, the data allegedly "is not statistically significant."

Applicant respectfully submits that the applicant does not have to provide evidence such that an asserted utility is true "beyond a reasonable doubt" *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). An applicant does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980). Instead, evidence will be sufficient if, considered as a whole, it leads a person of skill in the art to conclude that the asserted utility is more likely than not true (See MPEP 2107.2(VII)). Further, a certain amount of experimentation is permissible as long as it is not undue. The detailed description required under 37 CFR 1.71 (MPEP §608.01) must be in such particularity as to enable any person skilled in the art to make and use the claimed subject matter without involving **extensive** experimentation (emphasis added).

Notwithstanding this, applicant respectfully submits that the specification **does provide** evidence of statistical significance. For example, on page 70, lines 23-29, the specification teaches:

> the frequency of occurrence of the AKAP10-5 SNP in such a population was found to decrease with age, thus making the allele a potential morbidity susceptibility gene, a gene associated with increased mortality or both. Using the healthy database, it was found that the homozygote GG genotype drops in the elderly population (over >60 years), by a statistically significant amount, p=0.02.

Historically, the cutoff for statistical significance is usually taken as a result having a P-value of less than 0.05 (see Nicholls, *Bulletin of the Am. Meteor. Soc.* 81(5): 981-986 (2000) and National Information Center on Health Services Research & Health Care Technology (May 14, 1998). As shown above, the specification teaches that the homozygote GG genotype drops in the "over 60" population by a statistically significant amount, because the reported P-value is less than 0.05.

The data presented in Example 4 evidences this observation. The data shows that the GG genotype is observed in 16.1% (115 of the 713 subjects) of selected healthy individuals less than 40 years old and in 11.2% (79 of the 703 subjects) of selected healthy individuals over 60 years old. Using the VassarStats 2x2 contingency table at http://faculty.vassar.edu/lowry/odds2x2.html, cited by the Examiner, applicant entered the number of individuals having the GG genotype (115) as the "Condition Present" and the number of individuals not having the GG genotype (598) as the "Condition Absent" for Group 1 - individuals less than 40 years old. Applicant entered the number of individuals having the GG genotype (79) as the "Condition Present" and the number of individuals not having the GG genotype (624) as the "Condition Absent" for Group 2 - individuals over 60 years old. A copy of the results is provided in the supporting documents. The VassarStats program returned results showing a Yates Chi-Square P-value of 0.009 and a Pearson Chi-Square P-value of 0.007, both of which are significant (actually "highly significant" because the value is less than 0.01). Thus, the data in Example 4 supports the conclusion that the homozygote GG genotype drops in the elderly population (over 60 years old) by a statistically significant amount.

Further, the specification discloses that a statistical analysis of the differences in the frequency of the AKAP10-1 allelic variant with increasing age groups shows that the significance level for differences in the allelic frequency for

alleles between the "younger" and the "older" populations is p = 0.0009 and for genotypes is p = 0.003 (page 98, lines 12-16). Thus, the specification discloses that the differences in the allelic and the genotypic frequencies between the younger and older age groups for the AKAP10-1 allele have P-values less than 0.05. Hence, the specification as a whole discloses results where the differences in the frequency of the AKAP10 allelic variants with increasing age groups among healthy individuals **are** statistically significant, indicating that the AKAP10 allelic variants are associated with morbidity susceptibility, increased mortality, or both. Thus, in view of the totality of facts and reasoning disclosed in the specification and known to the skilled artisan, there is no showing by the Examiner to establish that is it more likely than not that one of skill in the art would doubt the truth of the asserted utility. Thus, the Examiner fails to establish a *prima facie* showing that the claimed subject matter lacks utility.

THE REJECTION OF CLAIMS 1-8, 11-20, 44-53, 69-71 and 75 35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 1-8, 11-20, 44-53, 69-71 and 75 are also rejected under 35 U.S.C. §112, first paragraph because the claims allegedly are not supported by either a substantial asserted utility or a well-established utility for the reasons set forth in the §101 rejection, and therefore one skilled in the art clearly would not know how to use the claimed invention. This rejection is respectfully traversed.

It is respectfully submitted that the specification teaches a specific, substantial and credible utility as set forth above in the response to the §101 rejection, and the specification teaches the skilled artisan how to use the claimed products and practice the claimed methods in accord with 35 U.S.C. §112. By virtue of compliance with 35 U.S.C. §101, the rejection of 35 U.S.C. §112, first paragraph is inapt.

REJECTION OF CLAIMS 6-8, 11-18, 44, 47-50, 69-71 and 75 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - WRITTEN DESCRIPTION

Claims 6-8, 11-18, 44, 47-50, 69-71 and 75 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed subject matter.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

The written description requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

Accordingly, a specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the application a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ

90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

When construing claim language, it is well-known that the phrase "consisting essentially of" is not the same as "comprising." The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, *e.g.*, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). Whereas, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original).

THE CLAIMS

Claim 6 is directed to an isolated nucleic acid molecule including at least 16 contiguous nucleotides of SEQ. ID. NO: 3, where the contiguous nucleotides include a sequence of 5 contiguous nucleotides as set forth from position 2069 to position 2077 of SEQ. ID. NO: 3. Claims 7 and 8 depend from claim 6 and are directed to various embodiments thereof.

Claim 11 is directed to a primer, probe or antisense nucleic acid molecule, including a sequence of at least 16 nucleotides that hybridizes under high stringency conditions adjacent to, or at a polymorphic region spanning, a position corresponding to position 2073 of SEQ ID No. 1 or SEQ ID No. 3, or the complement thereof, wherein high stringency conditions correspond to and include a wash step in 0.1 x SSPE, 0.1% SDS, at 65°C thereof. Claims 13-18 depend from claim 11 and are directed to various embodiments thereof.

Claim 44 is directed to a cell that includes heterologous nucleic acid that encodes a human AKAP10 variant protein or portion thereof that exhibits a biological activity of the full length variant protein, where the AKAP10 variant protein or portion thereof includes a polymorphism that results in a valine at a position corresponding to the position of amino acid residue 646 of SEQ ID NO: 2.

Claim 47 is directed to a kit that includes a first primer or probe of claim 11; and a second primer or probe that specifically hybridizes adjacent to or at a polymorphic region spanning a position corresponding to positions selected from the group consisting of position 83587 of SEQ ID NO 13 or 17, position 129600 of SEQ ID NO 14 or 17, and position 156,277 of SEQ ID NO 18 or 17 of an AKAP10 allele or the complement thereof. Claims 48-50 depend from claim 47 and are directed to various embodiments thereof.

Claim 69 is directed to a solid support that includes a nucleic acid of at least 16 nucleotides including a polymorphic region of an AKAP10 gene, where the polymorphic region includes a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand. Claims 70 and 71 depend from claim 69 and are directed to various embodiments thereof.

Claim 75 is directed to a primer that includes a sequence of nucleotides selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20, where the primer has a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to a position selected from the group consisting of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18.

ANALYSIS

The analysis for compliance with the written description requirement where claims are directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species?

Applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied.

Claims 6-8 and 15-18

With respect to claims 6-8 and 15-18, the Examiner alleges that the instant specification has not described a representative number of members within the very large genus of any isolated nucleic acid that includes 16, 30 or 50 contiguous nucleotides of SEQ ID NO:3 that includes 5 contiguous nucleotides from positions 2069-2077 of SEQ ID NO:3.

As a preliminary matter, applicant respectfully submits that claims 15-18, which ultimately depend from claim 11, are improperly included in the rejection directed to claims 6-8, and should be included in the rejection of claim 11, discussed below. Claims 6-8 are directed to an isolated nucleic acid molecule. Claims 15-18 are directed to the primer, probe or antisense molecule of claim 11.

The Claimed Genus

The Examiner alleges that the claims as written minimally include 16, 30 or 50 contiguous nucleotides of SEQ ID NO:3 embedded within a larger sequence. Applicant submits that the claimed genus includes isolated nucleic acid molecules that include 16, 30 or 50 contiguous nucleotides of SEQ ID NO:3 where the contiguous nucleotides include 5 contiguous nucleotides from positions 2069-2077 of SEQ ID NO:3.

Applying the Guidelines

a) The variation among members of the genus is not substantial. The specification teaches that those of skill in the art recognize common elements among the members of the claimed genus. For example, the specification teaches that the molecules are typically of a length such that they are statistically unique (*i.e.*, occur only once) in the genome of interest and that, for example, for a probe

or primer to be unique in the human genome, it contains at least 14, 16 or more contiguous nucleotides of a sequence complementary to or identical to a gene of interest (see page 39, lines 6-11). The specification teaches that nucleotide position 2073 of the AKAP10 gene coding sequence is located in the C-terminal PKA binding domain (see page 5, lines 3-8). Further, the specification discloses that the nucleotide sequence of the coding sequence of the allelic variant AKAP10-5 is presented as SEQ ID NO: 3 (page 6, lines 11-13) and that AKAP10-5 contains a previously undisclosed single nucleotide polymorphism (SNP), an A-to-G transition, at nucleotide position 2073 of the AKAP10 gene coding sequence that results in an Ile-to-Val substitution at the protein level for the AKAP10 gene protein product (see page 5, lines 2-8).

Thus, claims 6-8 include as common conserved elements (a) 16 contiguous nucleotides of SEQ.ID.NO:3, (b) within the 16 contiguous nucleotides, 5 contiguous nucleotides that include the C-terminal PKA binding domain (from position 2069 to position 2077 of SEQ.ID.NO:3) and (c) an SNP (A-to-G transition) at nucleotide position 2073 of the AKAP10 gene coding sequence. Hence, the nucleic acid molecules share several common conserved elements.

It is respectfully submitted that those of skill in the art would readily understand that as long as the nucleic acid molecule includes at least 16 contiguous nucleotides of SEQ ID NO:3 that contain 5 contiguous nucleotides from positions 2069-2077 of SEQ ID NO:3, numerous sequences readily can be combined with these fragments such that a multiplicity of sequences that include these fragments are described. It is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize those nucleic acid molecules within the scope of the instant claims, and how to use well-known techniques to form the multiplicity of sequences claimed. Hence, persons of skill in the art would have recognized that applicant was in possession of the subject matter claimed at the time of filing the application.

b) The specification provides a representative number of examples explicitly and implicitly by defining the requisite properties for the claimed nucleic acid molecules. With respect to the Examiner's allegation that "there is actual reduction to practice of a single disclosed species, namely SEQ. ID. NO:3", applicant respectfully submits that significantly more than "a single disclosed species" is disclosed in the specification. The Examiner is reminded that possession may be shown by describing actual reduction to practice of the claimed subject matter and filing of a patent application is a reduction to practice (M.P.E.P.§ 2163). Also, possession does not mean physical possession but appreciation. Using the parameters in the claims, even if only nucleic acid molecules having the minimum contiguous nucleotides of 16, 30 and 50 are considered, at least 15 isolated nucleic acid molecules are appreciated and thus disclosed, because there are at least five permutations of the sequence from position 2069 to 2077 whereby 5 contiguous nucleotides can be included (2069→2073, 2070→2074, 2071→2075, 2072→2076 and 2073→2077).

Applicant respectfully submits that the specification discloses several exemplary embodiments and the knowledge in the art allows a person of skill in the art to choose or produce several more nucleic acid molecules within the scope of the claimed composition. Thus, the specification provides adequate written description of all the requisite elements. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Claims 11-14, 47-50 and 69-71

With respect to claims 11-14, 15-18, 47-50 and 69-71, the traverse provided in the Amendment, sent August 25, 2003, is repeated and incorporated herein by reference. As indicated above, claims 15-18 depend from claim 11 and are addressed here. Claim 69-71, which are directed to solid supports, are separately discussed below.

The Examiner urges (page 19, lines 5-9) that Example 9 describes cDNA molecules that hybridize under highly stringent conditions and provide a function and thus are found to be described, but that the instant claims allegedly lack any particular function and are drawn to partial sequences and thus encompass large numbers of nucleic acids that allegedly have not been reduced to practice or described. Applicant respectfully submits that the written description includes Examples 1-6 only. There is no Example 9.

The Claims

Claim 11 requires that the primer, probe or antisense nucleic acid molecule include a sequence of at least 16 nucleotides that specifically hybridizes under high stringency conditions corresponding to 0.1 x SSPE, 0.1% SDS, 65°C adjacent to, or at a polymorphic region spanning, a position corresponding to position 2073 of SEQ ID No. 1 or SEQ ID No. 3 or the complement thereof. Claims 13-18 depend from claim 11 and are directed to various embodiments thereof. Claim 47 is directed to a kit that includes a first primer or probe of claim 11 and a second primer or probe that specifically hybridizes adjacent to or, at a polymorphic region spanning, a position corresponding to positions selected from a specific group of positions.

The Claimed Genus

The genus that encompasses the claimed subject matter is that which includes primer, probe and antisense nucleic acid molecules that include a sequence of at least 16 nucleotides that specifically hybridizes under high stringency conditions corresponding to 0.1 x SSPE, 0.1% SDS, 65°C adjacent to, or at a polymorphic region spanning, a position corresponding to position 2073 of SEQ ID No. 1 or SEQ ID No. 3 or the complement thereof.

Applying the Guidelines

a) The variation among members of the genus is not substantial. As discussed above, the specification teaches that the molecules are typically of a length such that they are statistically unique (*i.e.*, occur only once) in the genome of interest and that, for example, for a probe or primer to be unique in the human genome, contain at least 14, 16 or more contiguous nucleotides of a sequence

complementary to or identical to a gene of interest (see page 39, lines 6-11). The nucleic acid sequence of the probe, primer or antisense molecule is complementary to at least a portion of a target molecule that includes a particular structural similarity or identity corresponding to the sequence adjacent to or including position 2073 of SEQ ID NO:1 or 3 or the complement thereof. There must be sufficient complementarity to be able to hybridize therewith under conditions of "high stringency." It is well-known to those of skill in the art that the "high stringency conditions" require that the nucleotide sequences of the claimed primer, probe or antisense molecules correlate to a particular structural similarity or identity that is about 90% or more similar or identical. Thus, in view of the specification, it is respectfully submitted that those of skill in the art would readily understand that applicant was in possession of a group of nucleic acid molecules that are complementary to at least a portion of a target molecule that includes a particular structural similarity that is at least 90% identical to the sequence adjacent to or including position 2073 of SEQ ID NO:1 or 3 or the complement thereof.

b) The specification provides a representative number of examples explicitly (for example, page 93 discloses a primer including a sequence of nucleotides of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:19 or SEQ ID NO:20) and implicitly by defining the requisite properties for the claimed nucleic acid molecules. From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize those nucleic acid molecules within the scope of the instant claims, and how to use well-known techniques to form the multiplicity of sequences claimed. Numerous sequences could readily be made by combining with these fragments, such that applicant constructively possessed a multiplicity of sequences including these fragments at time of application. Thus, applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the claimed subject matter. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Alleged Lack of Function

Applicant respectfully submits that the claimed primer, probe and antisense nucleic acid molecules have many functions known to one of skill in this art, for example, for use in assays to detect the presence of a nucleic acid sequence complementary to at least a portion of the molecule and sufficiently complementary to be able to hybridize therewith. The specification explicitly teaches that the claimed primer, probe and antisense nucleic acid molecules are useful in detection methods, and that primers can be used to amplify at least a portion of a nucleic acid (see page 61, lines 4-12). The specification explicitly teaches that the claimed probes are useful for detecting a target sequence, such as in diagnostic methods (see page 61, lines 20-27). The specification teaches that the probes may be modified by the addition of a capture moiety or attached to a solid support for the capture and purification of any DNA or RNA hybridized thereto (see page 62, lines 11-15). In addition, the specification teaches that
the claimed nucleic acids (sense and antisense) are useful in diagnostic and prognostic methods for monitoring the activity of an AKAP10 protein, such as direct or indirect changes, increases or decreases of a biological activity attributed to AKAP10 protein (see page 36, lines 15-20). Hence, the claimed primer, probe and antisense nucleic acid molecules have many functions known to one of skill in this art.

Claim 44

The Examiner alleges that "the specification does not particular[ly] provide any additional variant proteins that exhibit a biological activity of the variant protein" and allegedly "fails to provide any biological activity information for the variant protein to constitute a function, therefore determining whether the portion exhibits a biological function has not been described." The Examiner alleges that the claim "does not require SEQ ID NO: 2, but merely requires [an] AKAP10 variant protein with a valine" and that the protein "may contain additional variants, mutations [and] truncations which have not been described."

Biological Activity

The specification explicitly defines the recitation "biological activity of an AKAP10 protein" on page 36, lines 21-26:

> As used herein, "biological activity of an AKAP10 protein" refers to, but is not limited to, binding of AKAP10 to protein kinase A or its subunits, localization of AKAP10 protein to a subcellular site, e.g., the mitochondria, localization of protein kinase A to the mitochondria and binding of AKAP10 protein to other proteins including other signalling enzymes.

In addition, it is respectfully submitted that the specification, at pages 87-89 clearly sets forth that the activity of an AKAP10 protein or portion thereof can be determined by examining signal transduction in the cell or by examining binding of AKAP10 protein or portion thereof to protein kinase A (or the RI and/or RII subunits thereof) or by examining cellular phosphorylation. Thus, the specification describes the biological function of an AKAP10 protein. Hence, it is respectfully submitted that one skilled in the art, in light of the teachings of the specification, would be able to determine whether a protein that corresponds to a portion of an AKAP10 variant protein exhibits a biological function.

Polymorphism

Claim 44 requires that the AKAP10 variant protein or biologically active portion thereof encoded by the heterologous nucleic acid include a polymorphism that results in a valine at a position corresponding to the position of amino acid residue 646 of SEQ ID NO:2. It is respectfully submitted that the claim does not require additional variants, mutations and/or truncations. Thus, although these additional features may be present with the claimed subject matter, because these features are not required by claim 44, a written description of these features is not required.

Applying the Guidelines

a) The variation among members of the genus is not substantial. Claim 44 is directed to a cell that includes heterologous nucleic acid that encodes a human AKAP10 variant protein or portion thereof that exhibits a biological activity of the full length variant protein, where the AKAP10 variant protein or portion

thereof includes a polymorphism that results in a valine substitution at a position corresponding to the position of amino acid residue 646 of SEQ ID NO: 2. The claim requires that the polymorphism results in a Val at a position corresponding to the position of amino acid residue 646 of SEQ ID NO: 2. The specification teaches and it is known to one skilled in this art that amino acid 646 of the human AKAP10 protein (SEQ. ID. NO: 2) is located in the carboxy-terminal region of the protein within a segment that participates in the binding of R-subunits of PKAs, and that this segment includes the carboxy-terminal 40 residues (page 42, lines 18-20). The carboxy-terminal 40 residues of the mouse D-AKAP2 protein are responsible for the interaction with the regulatory subunits of PKA, and this region is fairly well conserved between the mouse D-AKAP2 and human AKAP10 proteins (page 42, lines 4-7). Thus, the full length variant protein, or the claimed fragments encoded by the heterologous nucleic acid, must contain, within a segment that participates in the binding to PKA or to a subunit of PKAs, a Val at a position corresponding to residue 646 of SEQ ID NO:2. Hence, there are common conserved elements among the claimed AKAP10 variant proteins or fragments thereof. Therefore, there is not substantial variation among the species within the genus. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species.

b) The specification provides a number of examples of human AKAP10 variant proteins with SNPs. For example, the specification discloses an allele, designated AKAP10-5, which contains an A-to-G transition at nucleotide position 2073 of the AKAP10 gene coding sequence (page 5, lines 2-5). The specification also discloses allelic AKAP10 variants where the nucleotide at position 2073 is replaced with a T or a C (see page 6, lines 22-26). In addition, the specification discloses a number of other AKAP10 variant proteins with SNPs. For example, the specification discloses AKAP10-6, which contains a C-to-G transversion, at nucleotide position 83587 of the human chromosome 17 sequence (page 5, lines 8-11) and AKAP10-7, which contains a G-to-A transition at nucleotide position 129,600 of the human chromosome 17 sequence (page 5, lines 15-19). Also disclosed is AKAP10-1, which is an allelic variant with a T to C transversion at

nucleotide position 156,277 of the AKAP10 genomic clone (page 5, lines 22-25). Thus, the specification provides a number of exemplary nucleic acid sequences that encode a human AKAP10 variant protein.

Further, the specification provides adequate basis for numerous exemplary nucleic acids encoding fragments of AKAP10 having Val at a position corresponding to residue 646 of SEQ ID NO: 2. See, for example, the paragraph bridging page 78 and 79, which teaches:

> A. Expression of AKAP Protein
>
> The isolated nucleic acid encoding a full-length polymorphic human AKAP10 protein, **or a portion thereof, such as a fragment containing the site of the polymorphism [e.g., Val at residue 646 of SEQ ID NO:2]**, may be introduced into a vector for transfer into host cells. Fragments of the polymorphic human AKAP10 proteins can be produced by those skilled in the art, without undue experimentation, by eliminating portions of the coding sequence from the isolated nucleic acids encoding the full-length proteins. (emphasis added)

Likewise the specification provides examples of biological activities of the full length protein or fragments thereof having Val at the position corresponding to residue 646 of SEQ ID NO:2. See, for example, page 42, lines 10-21:

> Polymorphisms of AKAP genes that alter gene expression, regulation, protein structure and/or protein function are more likely to have a significant effect on the regulation of enzyme (particularly PKA) activity, cellular transduction of signals and responses thereto and on the basic functioning of cells than polymorphisms that do not alter gene and/or protein function. Included in the polymorphic AKAPs provided herein are human AKAP10 proteins containing differing amino acid residues at position number 646 of SEQ. ID. No. 2.
>
> Amino acid 646 of the human AKAP10 protein (SEQ. ID. NO: 2) is located in the carboxy-terminal region of the protein within a segment that participates in the binding of R-subunits of PKAs. This segment includes the carboxy-terminal 40 amino acids.

In view of the specification, those of skill in the art would readily understand that fragments of human AKAP10 protein that include a sequence corresponding to residue 646 of SEQ ID NO: 2 would have the biological activity of binding to PKA or to an R-subunit within PKA. Accordingly, it is respectfully submitted that the skilled artisan would clearly recognize that applicant was in possession of cells including heterologous nucleic acids encoding fragmented

portions of AKAP10 that exhibit a biological activity of the full length variant protein, such as PKA binding, RI subunit binding and/or RII subunit binding. In addition, it is respectfully submitted that the specification, at pages 87-89 clearly sets forth that the activity of an AKAP10 protein or portion thereof can be determined by examining signal transduction in the cell or by examining binding of AKAP10 protein or portion thereof to protein kinase A (or the RI and/or RII subunits thereof) or by examining cellular phosphorylation.

Therefore, because there is sufficient written description as to the necessary common attributes or features of the elements possessed by the members of the genus, and the specification provides examples of human AKAP10 variant proteins and biological activities of the full length protein or fragments thereof having Val at the position corresponding to residue 646 of SEQ ID NO:2, one skilled in the art would conclude that applicant had possession of the claimed subject matter at the time of filing of the application. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Claim 69

Claim 69 is directed to a solid support that includes a nucleic acid of at least 16 nucleotides that includes a polymorphic region of an AKAP10 gene, where the polymorphic region includes a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand.

The Claimed Genus

The genus that encompasses the claimed subject matter is that which includes solid supports having a nucleic acid of at least 16 nucleotides that includes a polymorphic region of an AKAP10 gene, where the polymorphic region includes a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand.

Applying the Guidelines

a) The variation among members of the genus is not substantial. The genus includes those solid supports that include a nucleic acid molecule with the claimed characteristics. For example, the nucleic acid molecules must have at

least 16 nucleotides. The specification teaches that, in the human genome, for a probe or primer to be unique, it should contain at least 14, 16 or more contiguous nucleotides of a sequence complementary to or identical to a gene of interest (see page 39, lines 6-11). The nucleic acids of the claimed genus include those that include a polymorphic region of an AKAP10 gene, and are further defined to require that the polymorphic region includes a nucleotide at a position corresponding to position 2073 of SEQ ID NO: 1 that is other than an A or other than T on the complementary strand. Hence, the nucleic acid molecules share several common conserved elements. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species.

b) The specification provides a number of examples of human AKAP10 variant proteins with SNPs located in the C-terminal PKA binding domain. For example, the specification discloses an allele, designated AKAP10-5, which contains an A-to-G transition at nucleotide position 2073 of the AKAP10 gene coding sequence (page 5, lines 2-5). The specification also discloses allelic AKAP10 variants where the nucleotide at position 2073 is replaced with a T or a C (see page 6, lines 22-26). The specification also implicitly provides examples by defining the requisite properties for the claimed nucleic acid molecules.

From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize those nucleic acid molecules within the scope of the instant claims, and how to use well-known techniques to form the multiplicity of sequences claimed. Numerous sequences could readily be made by combining with these fragments, such that applicant constructively possessed a multiplicity of sequences including these fragments at time of application. Thus, applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the claimed subject matter.

Claim 75

Regarding claim 75, Applicant respectfully disagrees with the Examiner's assertion that the

> nucleic acid reads on any oligonucleotide which comprises SEQ ID NO:8, 15, 29 and 20 which vary in length from 17-20 nucleotides. As discussed above, the partial structure embedded within a larger sequence is not representative of the entire genus, as exemplified by the art rejections below. (emphasis added)

The Examiner contends that "consisting essentially of" and "comprising" are equivalent, citing MPEP 2111.03, which states

> for the purposes of **searching** and for **applying art under 35 U.S.C. 102 and 103**, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising" (emphasis added).

Applicant respectfully submits that the instant rejection is raised under 35 U.S.C. §112, first paragraph, and is not raised under 35 U.S.C. 102 or 103. Hence, the citation of MPEP 2111.03 is not germane to this rejection. Further, applicant respectfully submits that the case law from which MPEP 211.03 is derived states:

> A "consisting essentially of" claim occupies a middle ground between closed claims that are written in a "consisting of" format and fully open claims that are drafted in a "comprising" format [*PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998) [other citations omitted].
>
> Other ingredients may also be present [], although not specifically identified in the claim, so long as those other unlisted ingredients do not have a material effect on the basic and novel characteristics of the [claimed subject matter]. *PPG*, 156 F.3d at 1354.
>
> [T]his court looked to the prosecution history of a patent to determine whether an unlisted ingredient was excluded from the scope of a "consisting essentially of" claim. Thus, PPG could have defined the scope of the phrase "consisting essentially of" for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.

Applicant respectfully submits that claim 75 and the specification provides "a clear indication . . . of what the basic and novel characteristics actually are."

Since the claim is examined as though it recites "comprising" and originally recited "comprising," the claim is amended herein to recite "comprising."

The Claimed Genus

Claim 75 is directed to a primer comprising a sequence of nucleotides selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20, where the primer has a free hydroxyl group for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18. Hence, the claimed subject matter is that which includes a nucleic acid primer having a free hydroxyl group for enzymatic extension through position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18 and that includes a sequence of nucleotides selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20. The claimed primers do not read on the full-length molecule since they include a 3′ hydroxyl for extension through specified loci that are not at the end of the molecule.

Applying the Guidelines

a) The variation among members of the genus is not substantial. The genus includes those primers that include a nucleic acid molecule with the claimed characteristics. Applicant respectfully submits that the application discloses, at page 61, lines 2-4 that

> Primers refer to nucleic acids which are capable of specifically hybridizing to a nucleic acid sequence which is adjacent to a polymorphic region of interest or to a polymorphic region and are extended. A primer can be used alone in a detection method, or a primer can be used together with at least one other primer or probe in a detection method. Primers can also be used to amplify at least a portion of a nucleic acid. For amplifying at least a portion of a nucleic acid, a forward primer (*i.e.*, 5′ primer) and a reverse primer (*i.e.*, 3′ primer) will preferably be used. Forward and reverse primers hybridize to complementary stands of a double stranded nucleic acid, such that upon extension from each primer, a double stranded nucleic acid is amplified.

One of skill in this art knows that primers include a free hydroxyl for DNA or RNA synthesis by the appropriate enzyme (see, for example, Patel *et al.*, page 87). The specification discloses extending the nucleic acid primer using the target nucleic acid as a template (for example, see page 13, lines 18-29). The claim requires that the free hydroxyl group be situated such that any enzymatic extension is through a polymorphic region of an AKAP10 gene corresponding to position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18, thereby fixing the 3' end of the primer. Each of these positions corresponds to the position of a disclosed SNP in an AKAP10 gene variant. For example, position 2073 of SEQ ID NO: 1 is the position of an SNP in the AKAP10 gene variant designated AKAP10-5.

The application is directed to a description of polymorphic AKAPs and nucleic acids encoding the AKAPs and provides a variety of methods to detect the presence of AKAP10 allelic variants and to identify them. In one embodiment, the specification discloses using primers for detection of polymorphisms, such as SNPs. For example, the specification discloses, at page 47, lines 5-17, that

> a primer is prepared that specifically hybridizes adjacent to a polymorphic site in a particular nucleic acid molecule. The primer is then extended in the presence of one or more dideoxynucleotides, typically with at least one of the dideoxynucleotides being the complement of the nucleotide that is polymorphic at the site. The primer and/or the dideoxynucleotides may be labeled to facilitate a determination of primer extension and identity of the extended nucleotide. In a preferred method, primer extension and/or the identity of the extended nucleotide(s) are determined by mass spectrometry (see, *e.g.*, PCT Application Nos. PCT/US96/03651 (WO96/29431), PCT Application No. PCT/US97/20444 (WO 98/20166), PCT Application No. PCT/US97/20194 (WO 98/20019), PCT Application No. PCT/US91/00046 (WO91/13075), and U.S. Patent Nos. 5,605,798, 5,622,824, 5,856,092.

Thus, the claimed primers hybridize to a target nucleic acid such that when enzymatically extended, the primer extension is through the polymorphic region. Hence, the claimed primers must be of a length sufficient to hybridize to the target nucleic acid, which encodes a known gene, and capable of being

enzymatically extended through a specified polymorphic region, which is disclosed in the application. Therefore, the claimed primers do not read on the full-length molecule nor do they evidence that applicant did not appreciate them at the time of filing.

It is respectfully submitted that those of skill in the art would readily understand that as long as the nucleic acid molecules include a sequence of nucleotides selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20, and further that the nucleic acid molecules include a free hydroxyl group for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18, numerous sequences readily can be combined such that a multiplicity of primers that include the claimed characteristics are described. It is not necessary to include in the specification that which those of skill in the art know. The specification is presumed to include all such knowledge. From the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize those nucleic acid molecules within the scope of the instant claims, and how to use well-known techniques to form the multiplicity of sequences claimed. Hence, persons of skill in the art would have recognized that applicant was in possession of the subject matter claimed at the time of filing the application.

b) The specification provides a representative number of examples explicitly (for example, page 93 discloses a primer including a sequence of nucleotides of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:19 or SEQ ID NO:20) and implicitly by defining the requisite properties for the claimed nucleic acid molecules. As discussed above, the claimed nucleic acid molecules are required to include a sequence of nucleotides selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20. Further,

the claimed nucleic acid molecules include a free hydroxyl group for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to position 2073 of SEQ ID NO: 1; position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17; position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17; or position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18. The specification discloses that the primers are generally of a length to be unique in the human genome, usually containing at least 14 or 16 contiguous nucleotides of a sequence complementary to or identical to a gene of interest, and can be 10, 20, 30, 50, 100 or more nucleic acids long (see page 39, lines 8-11).

Applicant respectfully submits that the specification provides a clear indication the claimed primers can include additional material. For example, the specification discloses, on page 53, lines 10-16, that

> By marking each of the allele-specific primers with a unique hapten, *i.e.* digoxigenin and fluorescein, each OLA reaction can be detected by using hapten specific antibodies that are labeled with different enzyme reporters, alkaline phosphatase or horseradish peroxidase. This system permits the detection of the two alleles using a high throughput format that leads to the production of two different colors.

Further, the specification, at page 62, lines 1-10, provides additional basis for primers containing additional material that does not materially affect the basic and novel characteristic of the claimed primer:

> Primers and probes (RNA, DNA (single-stranded or double-stranded), PNA and their analogs) described herein **may be labeled with any detectable reporter or signal moiety** including, but not limited to radioisotopes, enzymes, antigens, antibodies, spectrophotometric reagents, chemiluminescent reagents, fluorescent and any other light producing chemicals. Additionally, these [primers and] probes **may be modified without changing the substance of their purpose by terminal addition of nucleotides designed to incorporate restriction sites or other useful sequences**, proteins, signal generating ligands such as acridinium esters, and/or paramagnetic particles. (emphasis added)

Applicant respectfully submits that from the description in the specification and the knowledge available in the art, a skilled artisan would be able to recognize those nucleic acid molecules within the scope of the instant claims, and how to

use well-known techniques to form the primers as claimed. Primers could readily be made by combining a sequence of nucleotides that correspond to SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20 with other nucleic acid fragments, while maintaining a free hydroxyl group for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18. Therefore, applicant actually or constructively possessed a multiplicity of primers having the claimed characteristics at time of application. Thus, applicant respectfully submits that the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in possession of the claimed subject matter.

Hence, in view of the specification, those of skill in the art would clearly recognize that the applicant was in possession of primers comprising a sequence of nucleotides selected from the group consisting of SEQ ID NOs: 8, 15, 19 and 20, having a free hydroxyl group for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to a position selected from the group consisting of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18, and that such primers could be modified, for example, by labelling with a detectable reporter or signal moiety, or modified by incorporating a restriction site, as is well-known in the art, without materially affecting their ability to hybridize adjacent to or at a polymorphic region of a target nucleic acid and their ability to be extended.

THE REJECTION OF CLAIM 75 UNDER 35 U.S.C. §102 - Birren *et al.*

Claim 75 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Birren *et al.* (Genbank #AC005730; 10/98), because Birren *et al.* allegedly discloses every element of claim 75. The Examiner alleges that Birren *et al.*

> "teaches a nucleic acid clone from chromosome 17 which comprises all 18 nucleotides of SEQ ID NO:20. Nucleotides 1-18 of SEQ ID NO:20 are identical to positions 129,582-129,599 of the

chromosome 17 nucleic acid. Therefore, Birren teaches a nucleic acid comprising SEQ ID NO:20 as required by the instant claim."

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.* 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Further, the reference must describe the invention as claimed sufficiently to have placed a person of skill in the art in possession of the invention. Prior art does not anticipate a thing or process unless it is enabling; an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated *Columbia Broadcasting System v. Sylvania Elec. Products, Inc.*, 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) *cert. denied*, 396 U.S. 1061, 164 USPQ 321 (1970).

"Before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." *Titanium Metals Corp. v Mossinghoff*, 603 F.Supp. 87,0, 225 USPQ 673 (1984) quoting *In re Application of Le Grice*, 49 CCPA 1124, 301 F.2d 9333.

CLAIM 75

Claim 75 is directed to a primer that comprises a sequence of nucleotides selected from SEQ ID NO: 8, SEQ ID NO: 15, SEQ ID NO: 19 and SEQ ID NO: 20 **AND** having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene corresponding to a position selected from the group consisting of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18. Hence it is directed to nucleic acid molecules that must end at or before a defined polymorphism (or the complement of such molecule).

Disclosure of Birren *et al.*

Birren *et al.* discloses a 162,025 basepair linear DNA clone from human chromosome 17 that purports to represent the complete sequence of human chromosome 17. The sequence disclosed by Birren *et al.* in Genbank # AC005730 includes in the sequence a series of 18 contiguous nucleotides at positions 129,582-129,599 that is identical to the sequence set forth in SEQ ID NO:20. Birren *et al.* does not describe such molecule as a separate entity, nor disclose a DNA molecule containing less than the 162,0256 basepair clone nor a molecule that includes a 3' hydroxyl for enzymatic extension through any loci corresponding to position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18 (or the complement thereof).

ANALYSIS

The Genbank sequence disclosed by Birren *et al.* purports to represent the complete sequence of human chromosome 17. Birren *et al.* does not disclose an AKAP10 gene. Birren *et al.* does not disclose a sequence of 18 nucleotides at positions 129,582-129,599 as a primer for enzymatic extension through the recited polymorphic regions of the AKAP10 gene. Birren *et al.* does not disclose that position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position

156,277 of SEQ ID NO: 17 or SEQ ID NO: 18 correspond to polymorphic regions of an AKAP10 gene. The Birren *et al.* Genbank sequence discloses at least 30,000 nucleotides downstream of the 3' end of polymorphisms through which the claimed primer must extend. The presence of these nucleotides precludes the sequence from having a free hydroxyl for enzymatic extension at the position claimed.

Thus, Birren *et al.* does not disclose a primer having a free hydroxyl for extension through a polymorphic region of an AKAP10 gene selected from position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 and SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18. Therefore, because Birren *et al.* does not disclose every element of the subject matter claimed in claim 75, Birren *et al.* does not anticipate claim 75. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

THE REJECTION OF CLAIM 75 UNDER 35 U.S.C. §102 - Adams *et al.*

Claim 75 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Adams *et al.* (Genbank #AA331406; 4/97), because Adams *et al.* allegedly discloses every element of claim 75. The Examiner alleges that Adams discloses a nucleic acid molecule that includes all 19 nucleotides of SEQ ID NO:19, because nucleotides 1-19 of SEQ ID NO:19 are allegedly identical to positions 45-27 of the disclosed human nucleic acid. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

CLAIM 75

See related section above.

Disclosure of Adams *et al.* - Genbank #AA331406

The cited reference indicates that Genbank #AA331406 is included in a paper entitled "Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides of cDNA sequence" (Adams *et al.*, Nature 377(6547 Suppl.): 3-174 (1995)). Adams *et al.* discloses a 178 basepair linear

mRNA EST from human embryo. The sequence disclosed by Adams *et al.* in Genbank # AA331406 includes a sequence of 19 nucleotides at positions 45-27 that is identical to the sequence set forth at SEQ ID NO:19. Adams *et al.* does not describe such molecule as a separate entity, nor disclose a DNA molecule containing less than 178 basepairs nor a molecule that includes a 3' hydroxyl for enzymatic extension through loci corresponding to any of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18.

ANALYSIS

As discussed above, a reference does not anticipate a claim unless it describes the claimed subject matter with sufficient clarity and specificity so that one of ordinary skill in the relevant art could practice the claimed subject matter without assistance from the patent application claimed to have been anticipated. Adams *et al.* does not disclose that its sequence is that of an AKAP10 protein, nor does the reference identify the human AKAP gene. Adams *et al.* does not disclose any teaching concerning chromosome 17 nor any sequence of chromosome 17. Adams *et al.* fails to teach a human AKAP gene nor provide insights regarding the structure of the human gene encoding AKAP proteins or AKAP10 variant proteins or a biologically active portion thereof. Adams *et al.* does not disclose a nucleic acid molecule having a free hydroxyl for extension through a polymorphic region of an AKAP10 gene as claimed. The Genbank sequence disclosed by Adams *et al.* does not anticipate claim 75 because it fails to describe the claimed subject matter with sufficient clarity and specificity so that one skilled in the relevant art could practice the claimed subject matter without assistance from the instant application.

Further, Adams *et al.* does not disclose every element of the claimed subject matter. Adams *et al.* does not disclose a primer as instantly claimed having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene selected from position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 and SEQ ID NO: 17 or position 156,277 of SEQ ID NO: 17 and SEQ ID NO: 18. Adams *et al.* does not

describe a sequence of 19 nucleotides at positions 45-27 as a separate entity, nor disclose a DNA molecule containing less than 178 basepairs.

It is respectfully submitted that the sequence disclosed by Adams *et al.* includes 159 more nucleotides than SEQ ID NO:19, 26 of which are downstream of the 3' end of the claimed primer. The presence of these 26 nucleotides downstream of the 3' end indicates that there is no free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene as instantly claimed. Thus, the Genbank sequence disclosed by Adams *et al.* does not disclose every element of the subject matter of claim 75. Because Adams *et al.* does not disclose every element of claim 75, Adams *et al.* does not anticipate claim 75.

THE REJECTION OF CLAIM 75 UNDER 35 U.S.C. §102 - Adams *et al.*

Claim 75 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Adams *et al.* (Genbank #AA349877; 4/97), because Adams *et al.* allegedly discloses every element of claim 75. The Examiner alleges that Adams *et al.* discloses a nucleic acid that comprises all 18 nucleotides of SEQ ID NO:15, because nucleotides 1-18 of SEQ ID NO:15 are allegedly identical to positions 198-181 of the disclosed human nucleic acid. Therefore, Adams allegedly discloses a nucleic acid that includes SEQ ID NO:15 as in claim 75. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

CLAIM 75

See related section above.

Disclosure of Adams *et al.* - Genbank #AA349877

The cited reference indicates that Genbank #AA331406 is included in a paper entitled "3,400 expressed sequence tags identify diversity of transcripts from human brain" (Adams *et al.*, Nat. Genet. 4: 256-267 (1993)). Adams *et al.* discloses a 276 basepair linear mRNA EST from human infant brain. The sequence disclosed by Adams *et al.* in Genbank # AA349877 includes a sequence of 18 nucleotides at positions 198-181 that is identical to the sequence set forth at SEQ

ID NO:19. Adams *et al.* does not describe such molecule as a separate entity, nor disclose a DNA molecule containing less than 276 basepairs nor a primer for enzymatic extension through a locus corresponding to any of position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 or SEQ ID NO: 17 and position 156,277 of SEQ ID NO: 17 or SEQ ID NO: 18.

ANALYSIS

Adams *et al.* does not disclose that its sequence is that of an AKAP10 protein, nor does the reference identify the human AKAP gene. Adams *et al.* does not disclose any teaching concerning chromosome 17 nor any sequence of chromosome 17. Adams *et al.* fails to teach a human AKAP gene nor to provide insights regarding the structure of the human gene encoding AKAP proteins or AKAP10 variant proteins or biologically active portions thereof. Thus, the Genbank sequence disclosed by Adams *et al.* does not provide an enabling methodology for isolation of a nucleic acid molecule having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene. Thus, the reference does not place one of ordinary skill in the art in possession of a molecule having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene from the sequence disclosed by Adams *et al.*

Adams *et al.* does not disclose anything regarding the human AKAP10 gene and does not disclose an enabling methodology that might be successfully used to screen for nucleic acid that could be a primer for enzymatic extension through a polymorphic region of an AKAP10 gene. Only in light of the instant specification would one of ordinary skill in the art have been able to have used the cited art to have obtained a DNA molecule having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene. Hence, the Genbank sequence disclosed by Adams *et al.* does not anticipate claim 75 because it fails to describe the claimed subject matter with sufficient clarity and specificity so that one skilled in the relevant art could practice the claimed subject matter without assistance from the instant patent application.

Further, Adams *et al.* does not disclose every element of the claimed subject matter. Adams *et al.* does not disclose a primer as instantly claimed having a free hydroxyl for enzymatic extension through a polymorphic region of an AKAP10 gene at position 2073 of SEQ ID NO: 1, position 83587 of SEQ ID NO: 13 or SEQ ID NO: 17, position 129600 of SEQ ID NO: 14 and SEQ ID NO: 17 or position 156,277 of SEQ ID NO: 17 and SEQ ID NO: 18. The sequence disclosed by Adams *et al.* includes an additional 258 nucleotides, of which 180 nucleotides are downstream of the 3' end of the instantly claimed primer. The presence of these 180 nucleotides downstream of the 3' end precludes the presence of a free hydroxyl for extension at a position as instantly claimed. Thus, Adams *et al.* does not disclose every element of the subject matter of claim 75. Because Adams *et al.* does not disclose every element of claim 75, Adams *et al.* does not anticipate claim 75.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
FISH & RICHARDSON P.C.

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THE GeneEd GLOSSARY

THE DEFINITIVE GUIDE TO THE LANGUAGE OF BIOTECHNOLOGY

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How To Use This Book

This book was written for individuals who move, or benefit from, the bioscience industry. Whether you're a scientist, journalist, an executive in a large pharmaceutical company, or someone who can benefit from biotech drugs, this book will help you keep abreast of the changing biotechnology landscape. More importantly, this book was written for the individual who wants to learn more about the basics of the bioscience industry. The book contains abbreviated definitions of specific terms and longer definitions of basic terms that are essential to understanding the industry.

The essential definitions are contained at the beginning of this book. Readers who want to improve their understanding of the bioscience field should read through the essential definitions before delving into other terms.

Keeping Up With Change

Change in the life science industry is accelerating. New drugs and technologies are being developed. The bioscience language evolves as fast as the industry itself. A current and more comprehensive version of this glossary is available on-line at www.geneed.com.

transmitted together from parent to offspring.

Polymerase chain reaction (PCR)

A technique used to amplify or generate large amounts of replica DNA of a segment of any DNA whose "flanking" sequences are known. Oligonucleotide primers that bind these flanking sequences are used by an enzyme (*Taq* polymerase) to copy the sequence in-between the primers. Cycles of heat to break apart the DNA strands, cooling to allow the primers to bind, and heating again to allow the enzyme to copy the intervening sequence, lead to a doubling of the DNA present at each cycle. The reactions are typically carried out on a regulated heating block and consist of 30-35 cycles of repeated amplification of all the DNA. An amplification of a single DNA molecule for 30 cycles will give rise to $2^{30} = 1x10^9$ (a billion-fold) increase, allowing single molecules of "target" DNA to be amplified to microgram amounts. The target DNA may be of any origin.

Polymorphism

(Literally, many forms). The existence of a gene in a population in at least two different forms at a frequency far higher than that attributable to recurrent mutation alone. Variations in a population may be measured by determining the rate of mutation in polymorphic genes. (See SNPs.)

Polypeptide

A single chain of covalently attached amino acids joined by peptide bonds. A polypeptide chain usually folds into a compact, stable structure (a domain) that is a component (or all) of the final protein.

Positional cloning

A method used to define the location of a gene on a chromosome

and to use this information to identify and clone the gene. The location of the gene is determined by linkage analysis of genes from a large family containing afflicted and normal members. Family pedigree studies are used to identify linkages between the transmission of the disease gene and observable genetic markers. This information is then used to screen for the location of putative genes (by chromosomal jumping and walking). The full sequencing of the gene provides information regarding the characteristics and function of the gene product, and a potential explanation for the cause of the disease.

Post-transcriptional modification

Alterations, such as the splicing out of introns and the addition of a 5' cap and poly(A) 3'tail, made to pre-mRNA before it leaves the nucleus and becomes mature mRNA,.

Post-translational modification

Alterations made to a protein after its synthesis at the ribosome. These modifications, such as the addition of carbohydrate or fatty acid chains, may be critical to the function of the protein. (see glycosylation).

Primary sequence (protein)

The linear sequence of amino acids in a polypeptide or protein.

Primer

A short oligonucleotide that provides a free 3' hydroxyl for DNA or RNA synthesis by the appropriate polymerase enzyme (DNA polymerase or RNA polymerase).

Prion

An infectious agent proposed to be responsible for Bovine

transmitted together from parent to offspring.

Polymerase chain reaction (PCR)

A technique used to amplify or generate large amounts of replica DNA of a segment of any DNA whose "flanking" sequences are known. Oligonucleotide primers that bind these flanking sequences are used by an enzyme (*Taq* polymerase) to copy the sequence in-between the primers. Cycles of heat to break apart the DNA strands, cooling to allow the primers to bind, and heating again to allow the enzyme to copy the intervening sequence, lead to a doubling of the DNA present at each cycle. The reactions are typically carried out on a regulated heating block and consist of 30-35 cycles of repeated amplification of all the DNA. An amplification of a single DNA molecule for 30 cycles will give rise to $2^{30} = 1x10^9$ (a billion-fold) increase, allowing single molecules of "target" DNA to be amplified to microgram amounts. The target DNA may be of any origin.

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GENES

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Point mutations are substitutions of single base pairs.

Polarity refers to the effect of a mutation in one gene in influencing the expression (at transcription or translation) of subsequent genes in the same transcription unit.

Polyadenylation is the addition of a sequence of polyadenylic acid to the 3′ end of a eucaryotic RNA after its transcription.

Polycistronic mRNA includes coding regions representing more than one gene.

Polymorphism refers to the simultaneous occurrence in the population of genomes showing allelic variations (as seen either in alleles producing different phenotypes or—for example—in changes in DNA affecting the restriction pattern).

Polyploid cell has more than two sets of the haploid genome.

Polyprotein is a gene product that is cleaved into several independent proteins.

Polysome (polyribosome) is an mRNA associated with a series of ribosomes engaged in translation.

Polytene chromosomes are generated by successive replications of a chromosome set without separation of the replicas.

Position effect refers to a change in the expression of a gene brought about by its translocation to a new site in the genome; for example, a previously active gene may become inactive if placed near heterochromatin.

Positive regulator proteins are required for the activation of a transcription unit.

Positive supercoiling describes the coiling of the double helix in space in the same direction as the winding of the two strands of the double helix itself.

Postmeiotic segregation describes the segregation of two strands of a duplex DNA that bear different information (created by heteroduplex formation during meiosis) when a subsequent replication allows the strands to separate.

Pribnow box is the consensus sequence TATAATG centered about 10 bp before the startpoint of bacterial genes. It is a part of the promoter especially important in binding RNA polymerase.

Primary transcript is the original unmodified RNA product corresponding to a transcription unit.

Primer is a short sequence (often of RNA) that is paired with one strand of DNA and provides a free 3′-OH end at which a DNA polymerase starts synthesis of a deoxyribonucleotide chain.

Primosome describes the complex of proteins involved in the priming action that initiates synthesis of each Okazaki fragment during discontinuous DNA replication; the primosome may move along DNA to engage in successive priming events.

Procaryotic organisms (bacteria) lack nuclei.

Processive enzymes continue to act on a particular substrate, that is, do not dissociate between repetitions of the catalytic event.

Promoter is a region of DNA involved in binding of RNA polymerase to initiate transcription.

Proofreading refers to any mechanism for correcting errors in protein or nucleic acid synthesis that involves scrutiny of individual units *after* they have been added to the chain.

Prophage is a phage genome covalently integrated as a linear part of the bacterial chromosome.

Provirus is a duplex DNA sequence in the eucaryotic chromosome corresponding to the genome of an RNA retrovirus.

Pseudogenes are inactive but stable components of the genome derived by mutation of an ancestral active gene.

Puff is an expansion of a band of a polytene chromosome associated with the synthesis of RNA at some locus in the band.

Pulse-chase experiments are performed by incubating cells very briefly with a radioactively labeled precursor (of some pathway or macromolecule); then the fate of the label is followed during a subsequent incubation with a nonlabeled precursor.

Quick-stop *dna* mutants of *E. coli* cease replication immediately when the temperature is increased to 42°C.

R loop is the structure formed when an RNA strand hybridizes with its complementary strand in a DNA duplex, thereby displacing the original strand of DNA in the form of a loop extending over the region of hybridization.

Rapid lysis (*r*) mutants display a change in the pattern of lysis of *E. coli* at the end of an infection by a T-even phage.

Reading frame is one of three possible ways of reading a nucleotide sequence as a series of triplets.

Reassociation of DNA describes the pairing of complementary single strands to form a double helix.

RecA is the product of the *recA* locus of *E. coli;* a protein with dual activities, acting as a protease and also able to exchange single strands of DNA molecules. The protease activity controls the SOS response; the nucleic acid handling facility is involved in recombination-repair pathways.

Recessive allele is obscured in the phenotype of a heterozygote by the dominant allele, often due to inactivity or absence of the product of the recessive allele.

HEALTHY PEOPLE 2000

Statistical Notes

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Number 23

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Trends in Racial and Ethnic-Specific Rates for the Health Status Indicators: United States, 1990–98

Kenneth G. Keppel, Ph.D.; Jeffrey N. Pearcy, M.S.; and Diane K. Wagener, Ph.D.

Abstract

The Health Status Indicators (HSIs) were developed as part of the Healthy People 2000 process to facilitate the comparison of health status measures at national, State, and local levels (1). In this report national trends in racial and ethnic-specific rates for 17 HSIs are examined for the period from 1990–98. One of three overarching goals of Healthy People 2000 was to reduce health disparities (2). Examination of trends in the HSIs indicates that rates for most racial/ethnic groups improved. Rates for American Indian or Alaska Natives did not improve for six of the HSIs. An index of disparity, a summary measure of disparity among race/ethnic-specific rates, was used to measure changes in disparity between 1990 and 1998. The index of disparity decreased for 12 of the HSIs. Based on this index, racial/ethnic disparity in the percent of low birthweight infants declined by 19 percent, disparity in the percent of children under 18 years of age in poverty and in the syphilis case rate declined by 13 percent, and disparity in the stroke death rate declined by 11 percent. The index declined by less than 10 percent for eight other indicators. The index of disparity increased between 1990 and 1998 for the other five HSIs examined here. The index of disparity increased by more than 10 percent for work-related injury death rates, motor vehicle crash death rates, and suicide death rates. While rates for the HSIs have improved, not all groups have benefited equally and substantial differences among racial/ethnic groups persist.

Introduction

Healthy People 2000 National Health Promotion and Disease Prevention Objectives, Objective 22.1 called for the development of a set of Health Status Indicators (HSIs) appropriate for use by Federal, State, and local health agencies (2). Under the auspices of the Centers for Disease Control and Prevention, a group of public health professionals, known as Committee 22.1, was convened to identify a set of HSIs. Through a rigorous consensus process, a list of 18 HSIs was developed and published in 1991 (1). Originally Committee 22.1 recommended that only one indicator, infant mortality, be examined by race and Hispanic origin. However, experience with the indicators soon revealed that it was essential to account for differences in the racial and ethnic composition of geographic areas when making comparisons. Committee 22.1 subsequently recommended that whenever data were available to provide reliable estimates, the HSIs be examined for specific groups (3). The first report on racial differentials in the HSIs at the national level was published in 1995 (4) and subsequent national data on the HSIs have been published in each *Healthy People 2000 Review* (5).

This report examines trends in the rates for 17 indicators associated with the original list of 18 HSIs. The original HSI for cardiovascular disease deaths was subdivided into two indicators, one for heart disease deaths and one for stroke deaths. Reported cases of Acquired Immunodeficiency Syndrome (AIDS) were excluded from this report because the case definition of AIDS changed in 1993 and because the transition from HIV infection to AIDS has been altered

substantially, making AIDS cases an inappropriate indicator of HIV infection. Reported cases of measles were excluded from this report because race was poorly reported during the earlier part of the period and the number of cases is now too small to make it practical to calculate rates by race/ethnicity. Rates or percents are shown for five racial/ethnic groups (white non-Hispanic, black non-Hispanic, Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander) from 1990 to 1998. Where appropriate, the data for the HSIs are age adjusted to control for differences in age composition among the racial/ethnic groups. Differences in race/ethnic-specific rates are affected by the quality of race and ethnic information reported in vital registration and case reporting systems as well as in the census. The quality of racial and ethnic data is known to vary (6), however, the effect on the findings presented here cannot be specified.

When the HSIs were developed, no target rates or percents were specified for the year 2000. However, many of the HSIs correspond to Healthy People 2000 objectives for which targets for the year 2000 were set. These targets were set to encourage significant improvement in rates for the total population by the year 2000. For some objectives, targets were also set for special population subgroups when it was known that these groups had higher rates than the total population. These targets called for a greater percent change for the minority population, with the aim of reducing the relative difference between rates for these racial/ethnic groups and the rate for the total population. Special population targets were established for Healthy People 2000 objectives that correspond closely to 10 of the HSIs, including the following:

- Stroke death rates among blacks
- Lung cancer death rates among black males
- Breast cancer death rates among black females
- Suicide death rates among American Indian or Alaska Native males and for white males 65 years of age and over
- Homicide death rates among black males 15–34 years of age, among Hispanic males 15–34, among black females 15–34, and among American Indian or Alaska Natives of all ages
- Tuberculosis case rates among blacks, Hispanics, American Indian or Alaska Natives, and Asian or Pacific Islanders
- Syphilis case rates among blacks
- Infant mortality rates among black, American Indian or Alaska Native, and Puerto Rican women
- Percent of low birthweight infants among black and Puerto Rican women
- Percent of women not beginning prenatal care in the first trimester among black, American Indian or Alaska Native, and Hispanic women

There were no corresponding special population targets for the following HSIs: Total death rates, heart disease death rates, motor vehicle crash death rates, work-related injury death rates, live birth rates for women age 15–17 years, percent of children under age 18 years living in poverty, and the percent of persons in counties with poor air quality.

The figures showing trends in the HSIs in this report are based on annual rates or percents for each of the five racial/ethnic groups. The vertical axis for the rate or percent in each figure is shown on a log scale. The log scale makes it possible to determine visually whether the rates are changing proportionally (parallel lines) or disproportionally over time. The trends in race/ethnic-specific rates are also discussed in terms of the relative change in rates from the beginning to the end of the period. The percent change in the rate for each specific group is calculated by subtracting the rate in 1998 from the rate in 1990, dividing by the rate in 1990 and expressing the result as a percent. Changes from 1990 to 1998 for the five racial/ethnic groups were compared in this way. These comparisons indicate whether the five groups are changing in the same direction and to the same extent. The ratios of highest to lowest race/ethnic-specific rates at the beginning and end of the period are also compared. These ratio comparisons indicate whether the proportional difference between the highest and lowest rates in 1998 was smaller or larger than the difference in 1990.

The special population targets were set to achieve relatively greater reductions in rates for specific populations compared to the total population. In order to determine whether or not greater reductions had occurred, the percent change from 1990 to 1998 for the special population (or a group representing the special population) was compared with the change for the total population. In order to be consistent with the intent of the special population target, the change in the special population should be greater than the change for the total population.

Finally, the index of disparity was employed as a summary measure of racial and ethnic disparity for each HSI in 1990 and 1998. The index of disparity was used to compare the degree of disparity in each indicator in 1990 with the degree of disparity in 1998. The index of disparity was also employed to compare the degree of disparity among HSIs in 1998. For additional information about the HSIs and the techniques employed in this report see the section on "Methods."

Findings

Infant mortality rate

Infant mortality rates from the linked files of live births and infant deaths are shown in figure 1. These rates are based on the race and origin of the mother recorded on the birth certificate. Linked files were not created for the years 1992–94. Infants of Asian or Pacific Islander women had the lowest infant mortality rates and infants of black non-Hispanic women had the highest infant mortality rates for the years shown. Between 1990 and 1998 the infant mortality rate for infants of American Indian or Alaska Native women declined by 29 percent, for infants of Hispanic women by 23 percent, for infants of black non-Hispanic women by 18 percent, and for infants of white

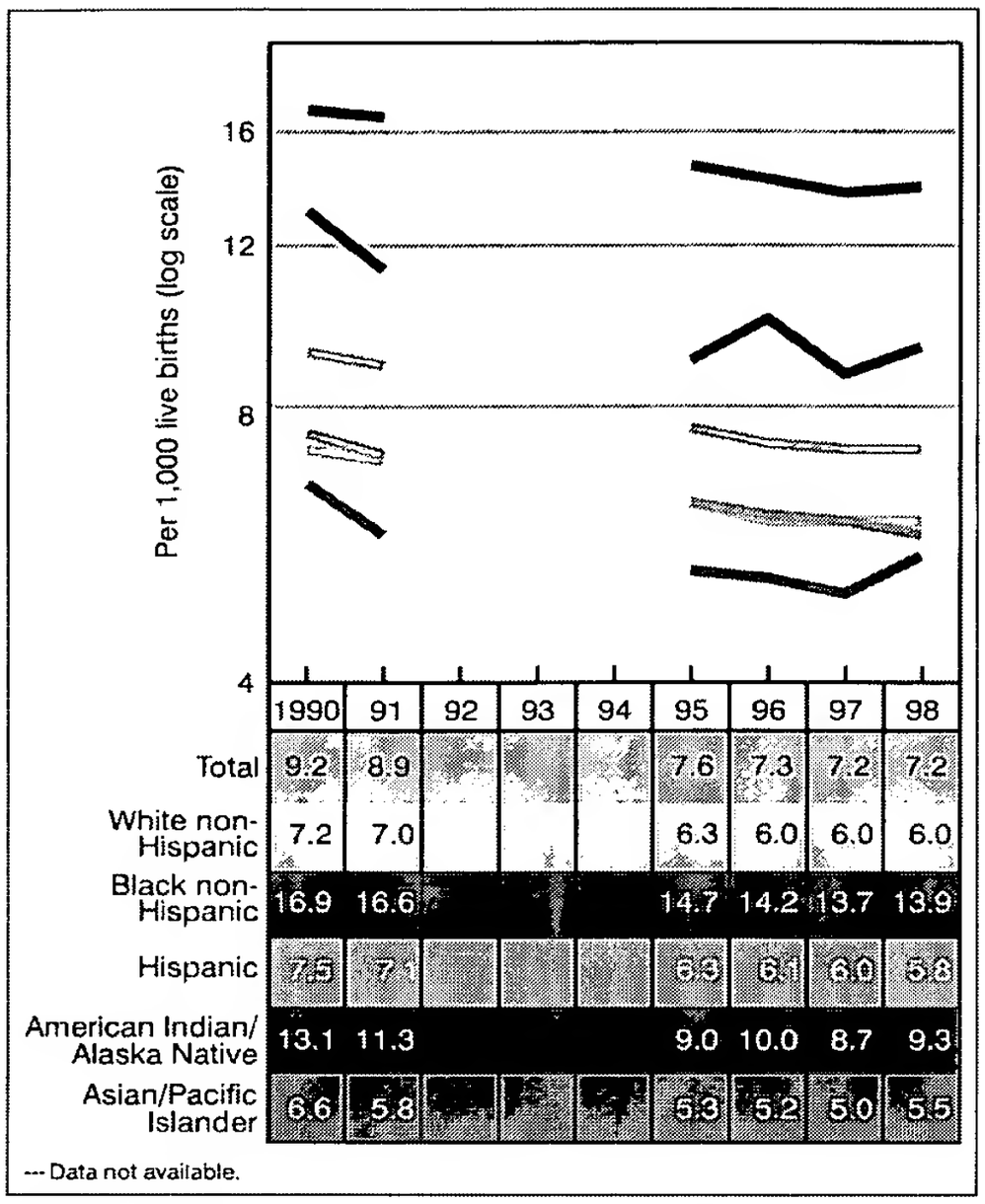


Figure 1. Infant mortality rates by race and Hispanic origin of mother: United States, 1990–91 and 1995–98

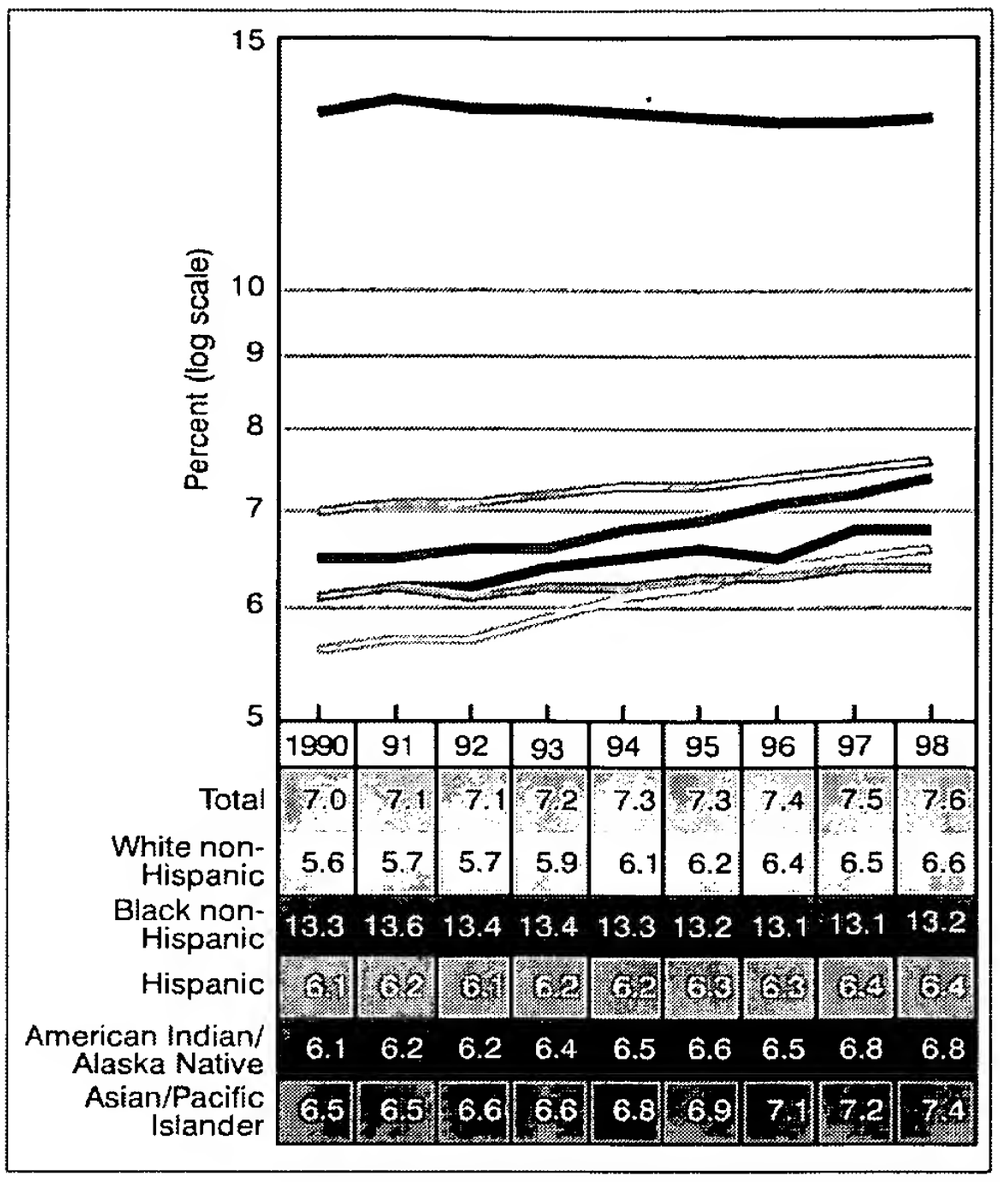


Figure 2. Percent low birthweight by race and Hispanic origin of mother: United States, 1990–98

non-Hispanic and Asian or Pacific Islander women by 17 percent.

In 1990 the infant mortality rate for infants of black non-Hispanic women was 2.6 times the rate for infants of Asian or Pacific Islanders. In 1998 the rate for infants of black non-Hispanic women was 2.5 times the rate for infants of Asian or Pacific Islanders.

The infant mortality rate for the total population declined by 22 percent from 9.2 per 1,000 live births in 1990 to 7.2 in 1998. Greater declines among infants of American Indian or Alaska Native women and among infants of Hispanic women compared with the total population were consistent with the special population target for Objective 14.1 for infants of American Indian or Alaska Native women and for infants of Puerto Rican women. A smaller decline of 18 percent for infants of black non-Hispanic women was inconsistent with the intent of the special population target for infants of black women.

Percent low birthweight

The percent of low birthweight infants among black non-Hispanic women was 13.3 in 1990 and 13.2 in 1998 (figure 2). The rates for the other four racial/ethnic groups increased, by 18 percent for white non-Hispanics, by 5 percent for Hispanics, by 11 percent for American Indian or Alaska Natives, and by 14 percent for Asian or Pacific Islanders. The differences between the black non-Hispanic group and the other groups decreased due to increases in rates for the other groups. In this instance, a reduction in racial/ethnic differences occurred despite the fact that the indicator was not declining to meet the Healthy People 2000 target for Objective 14.5 of 5 percent.

The ratio of the percent low birthweight for the highest group in 1990 (13.3 percent) to the percent for the lowest group (5.6 percent) was 2.4. In 1998 the ratio was 2.1. The relative difference between the highest and lowest rates was, therefore, reduced during the period.

The fact that the percent of low birthweight infants did not decline for Hispanic women and declined by less than 1 percent for black non-Hispanic women is not consistent with special population targets for Puerto Rican and black women.

Women with no prenatal care in the first trimester

In 1990 the proportion of women with no prenatal care in the first trimester ranged from 16.7 percent for white non-Hispanic women to 42.1 percent for American Indian or Alaska Native women (figure 3). In 1998 the range was from 12.1 percent for white non-Hispanic women to 31.2 percent for American Indian or Alaska Native women. The percent of women with no prenatal care in the first trimester decreased for all five groups from 26 to 35 percent

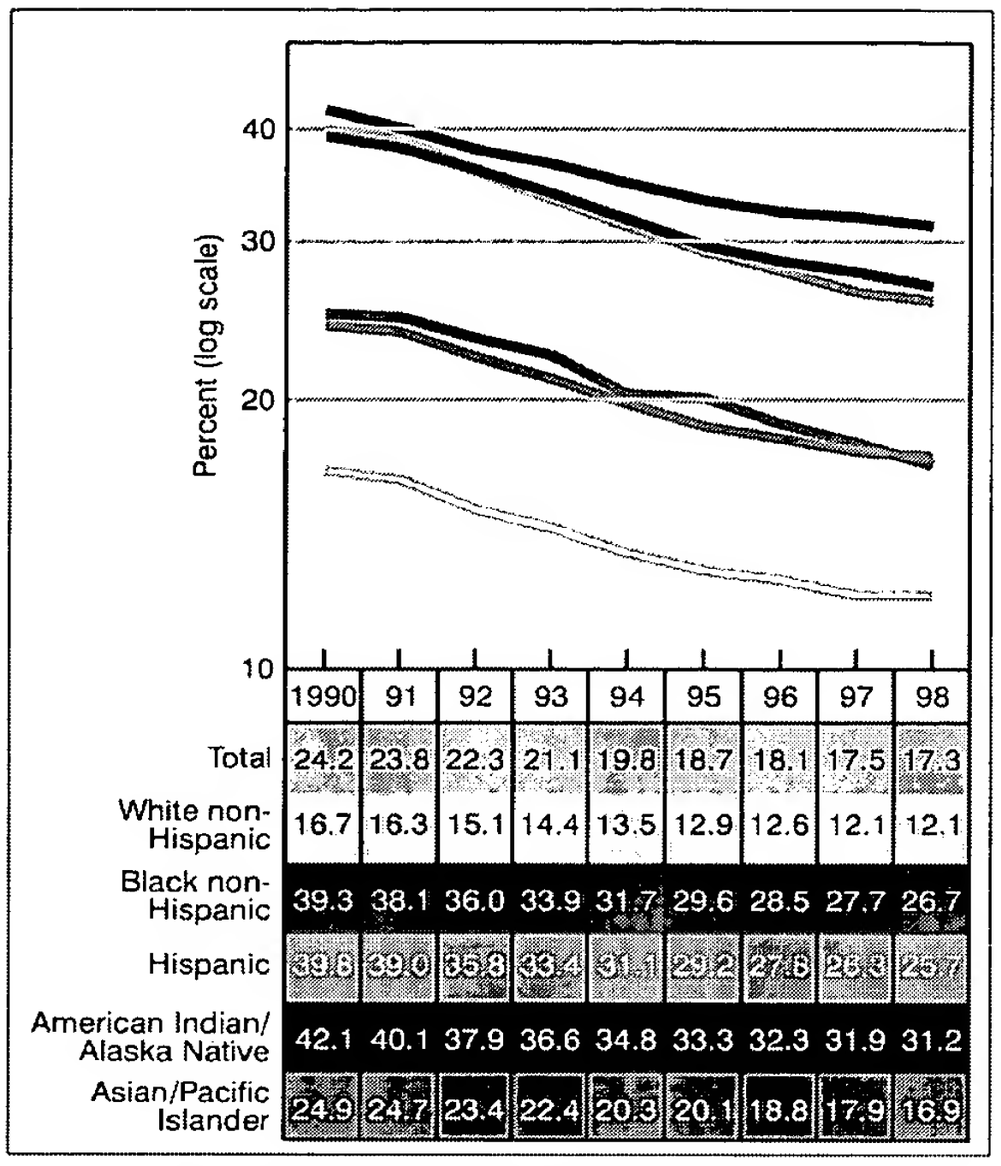


Figure 3. Percent of women with no prenatal care in the first trimester by race and Hispanic origin of mother: United States, 1990–98

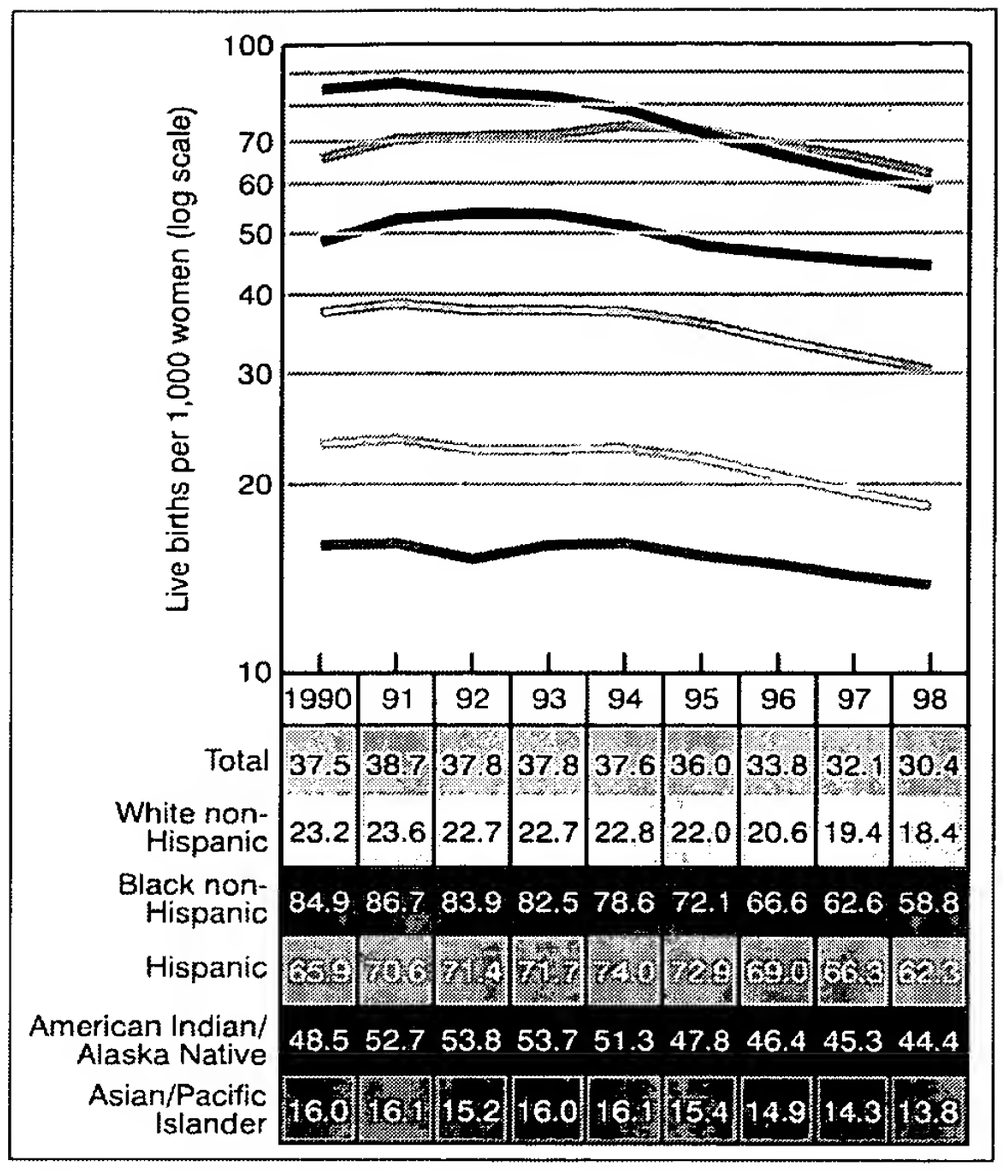


Figure 4. Live birth rates for women age 15–17 years by race and Hispanic origin of mother: United States, 1990–98

during the period. American Indian or Alaska Native women, the group with the highest percent of women with no care in the first trimester, had the least decline (26 percent). Little convergence in rates is evident in figure 3.

The percent of women without prenatal care in the first trimester for American Indian or Alaska Natives was 2.5 times the percent for white non-Hispanics in 1990. In 1998 the percent for American Indian or Alaska Native women was 2.6 times the rate for white non-Hispanics. The relative difference between the groups with the highest and lowest percents was essentially unchanged.

The percent of women with no prenatal care in the first trimester for the total population decreased by 29 percent from 24.2 percent in 1990 to 17.2 percent in 1998. The rates for black non-Hispanics, Hispanics, and Asian or Pacific Islanders declined by greater margins (32 percent, 35 percent, and 32 percent, respectively). These declines are consistent with special population targets for blacks and Hispanics in Objective 14.11. The percent of women not beginning prenatal care in the first trimester declined by 26 percent for American Indian or Alaska Native women, which was inconsistent with the intent of the special population target for this group.

Live birth rates for females age 15–17 years

The live birth rate for females age 15–17 years is based on the number of live births to females age 15–17 in the numerator and the estimated number of females age 15–17 in the denominator based on the 1990 census and intercensal estimates. The fact that the numerator and denominator of the rate are based on different data systems increases the potential effect of errors in racial and ethnic classification. There are no routine estimates of the net effect of these errors for this population (see the section on Race and Hispanic origin under "Methods").

Among black non-Hispanic women 15–17 years of age, a decline in live birth rates began after 1991 (figure 4). Among American Indian or Alaska Natives, declines in live birth rates began after 1992. Among white non-Hispanics, Hispanics, and Asian or Pacific Islanders, declines in live birth rates for females age 15–17 years began after 1994. As a result of the delay in the start of the decline for young Hispanic women, their live birth rates surpassed those of black non-Hispanic women after 1994. Between 1990 and 1998, live birth rates for females age 15–17 years declined by 31 percent for black non-Hispanics, by 21 percent for white non-Hispanics, by 14 percent for Asian or Pacific Islanders, by 8 percent for American Indian or Alaska Natives, and by 5 percent for Hispanics.

The highest race/ethnic-specific group rate in 1990 was 5.3 times the lowest group rate, whereas the highest group rate in 1998 was 4.5 times the lowest rate. Some convergence in rates is evident in figure 4.

Total death rate

The HSIs include the age-adjusted total death rate and age-adjusted death rates for seven specific causes of death. Race/ethnic-specific death rates are subject to misclassification of race and ethnicity among deaths and misclassification of individuals in the census and consequent errors in intercensal estimates. Estimates of the approximate effect of the combined bias due to race misclassification on death certificates and under enumeration on the 1990 census are as follows: white, –1.0 percent; black, –5.0 percent; American Indian, +20.6 percent; and Asian or Pacific Islander, +10.7 percent. The findings presented here should be interpreted with the limitations of the data in mind. For additional discussion of classification issues see the section on Race and Hispanic origin under "Methods" below.

Age-adjusted death rates for the HSIs are shown in table 1 for 1990 and for 1998. The percent change in each race/ethnic-specific rate between 1990 and 1998 is shown along with the ratio of the highest race/ethnic-specific rate to the lowest race/ethnic-specific rate for each year. In 1990 Asian or Pacific Islanders had the lowest total age-adjusted death rate, 295.5 deaths per 100,000 population. The rates for Hispanics, American Indian or Alaska Natives, and white non-Hispanics ranged from 395.2 to 483.7 per 100,000. Non-Hispanic blacks had the highest rate (785.2 per 100,000). The rates for all groups except American Indian or Alaska Natives were lower in 1998 than they were in 1990. The two groups with the lowest rates declined by the greatest proportions; the rates for Asian or Pacific Islanders declined by 10 percent and the rates for Hispanics declined by 13 percent. During the same period, the groups with the

Table 1. Age-adjusted death rates for selected causes of death by race and Hispanic origin, 1990, 1998, and percent change from 1990 to 1998: United States

		Non-Hispanic					
	Total	White	Black	Hispanic	American Indian or Alaska Native	Asian or Pacific Islander	Ratio highest/lowest[2]
Total deaths							
1990[1]	518.0	483.7	785.2	395.2	441.7	295.5	2.7
1998	471.7	452.7	710.7	342.8	458.1	264.6	2.7
Percent change, 1990–98	–8.9	–6.4	–9.5	–13.3	3.7	–10.5	
Heart disease							
1990[1]	151.3	145.3	211.8	101.5	106.0	78.0	2.7
1998	126.6	123.6	188.0	84.2	97.1	67.4	2.8
Percent change, 1990–98	–16.3	–14.9	–11.2	–17.0	–8.4	–13.6	
Stroke							
1990[1]	27.5	25.1	47.8	20.7	19.1	24.7	2.5
1998	25.1	23.3	42.5	19.0	19.6	22.7	2.2
Percent change, 1990–98	–9.0	–7.2	–11.1	–8.2	2.6	–8.1	
Lung cancer							
1990[1]	39.8	39.8	50.9	15.7	19.6	17.6	3.2
1998	37.0	38.3	46.0	13.6	25.1	17.2	3.4
Percent change, 1990–98	–7.0	–3.8	–9.6	–13.4	28.1	–2.3	
Female breast cancer							
1990[1]	23.0	23.0	27.3	14.0	9.9	9.9	2.8
1998	18.8	18.7	26.1	12.1	10.3	9.8	2.7
Percent change, 1990–98	–18.3	–18.7	–4.4	–13.6	4.0	–1.0	
Motor vehicle crash							
1990[1]	18.4	18.1	18.3	19.2	33.0	12.5	2.6
1998	15.6	15.7	17.2	14.9	31.8	8.6	3.7
Percent change, 1990–98	–15.2	–13.3	–6.0	–22.4	–3.6	–31.2	
Suicide							
1990[1]	11.5	12.5	7.0	7.2	12.4	6.0	2.1
1998	10.4	11.8	6.1	6.0	13.4	5.9	2.3
Percent change, 1990–98	–9.6	–5.6	–12.9	–16.7	8.1	–1.7	
Homicide							
1990[1]	10.2	4.1	39.6	17.5	11.1	5.2	9.7
1998	7.3	3.2	26.1	9.9	9.9	3.7	8.2
Percent change, 1990–98	–28.4	–22.0	–34.1	–43.4	–10.8	–28.8	

[1] Age-adjusted death rates for 1990 were calculated based on population estimates for July 1, 1990. Rates published elsewhere for 1990 are based on the enumerated population on April 1, 1990, for the year in which the decennial census was taken. Rates for noncensus years are based on July 1 (midyear) populations. In order to measure changes over time, rates based on the July 1 populations are used.

[2] Ratio of the highest race/ethnic-specific rate to the lowest race/ethnic-specific rate for each year.

highest rates (white non-Hispanics and black non-Hispanics) declined by 6 percent and 9 percent, respectively. The rates for American Indian or Alaska Natives increased by 4 percent from 1990 to 1998.

In 1990 the highest group rate (black non-Hispanic, 785.2 per 100,000) was 2.7 times the lowest group rate (Asian or Pacific Islander, 295.5 per 100,000) and in 1998 the highest group rate (black non-Hispanic, 710.7 per 100,000) was again 2.7 times the lowest group rate (Asian or Pacific Islander, 264.6 per 100,000). Although the absolute difference between the highest and lowest group rates in 1998 was smaller than the difference in 1990 (446.1 versus 489.7), the proportional difference between the highest and lowest rates was unchanged.

Heart disease death rate

Between 1990 and 1998 all five racial/ethnic groups experienced declines in age-adjusted heart disease death rates (table 1). Rates declined by 17 percent for Hispanics, by 15 percent for white non-Hispanics, by 14 percent for Asian or Pacific Islanders, by 11 percent for black non-Hispanics, and by 8 percent for American Indian or Alaska Natives.

In 1990 the age-adjusted heart disease death rate for black non-Hispanics (211.8 per 100,000) was 2.7 times the rate for Asian or Pacific Islanders (78.0 per 100,000). In 1998 the rate for black non-Hispanics (188.0 per 100,000) was 2.8 times the rate for Asian or Pacific Islanders (67.4 per 100,000). The ratios of heart disease death rates for the groups with the highest and lowest rates at the beginning and end of the period were essentially the same. All five groups experienced reductions in heart disease death rates ranging from 8 to 17 percent. Therefore, there was little reduction in the relative differences among racial/ethnic groups.

Stroke death rate

The age-adjusted stroke death rate was substantially higher for black non-Hispanics compared with the other racial/ethnic groups (table 1). Between 1990 and 1998 the rate for American Indian or Alaska Natives increased by 3 percent; however, this difference was not statistically significant. The rates for the other four racial/ethnic groups declined by 7 to 11 percent.

In 1990 American Indian or Alaska Natives had the lowest age-adjusted death rate due to stroke (19.1 per 100,000) while the rate for black non-Hispanics was 2.5 times as high (47.8 per 100,000). In 1998 Hispanics had the lowest age-adjusted death rate due to stroke (19.0 per 100,000). In 1998 the rate for black non-Hispanics was 2.2 times the rate for Hispanics. The relative difference between the highest and lowest rates had, therefore, decreased.

The Healthy People 2000 target for Objective 15.2 called for a 34 percent reduction in the age-adjusted stroke death rate for the total population and a 49 percent reduction in the rate for blacks from the baseline in 1987 to the year 2000 target. Between 1990 and 1998 the stroke death rates for black non-Hispanics decreased by 11 percent. During the same period the age-adjusted stroke death rate for the total population decreased by 9 percent from 27.5 to 25.1 per 100,000. The actual reduction for blacks was slightly greater than that for the total population.

Lung cancer death rate

Hispanics had the lowest age-adjusted death rate due to lung cancer in 1990 (table 1). Asian or Pacific Islanders, American Indian or Alaska Natives, white non-Hispanics, and black non-Hispanics had successively higher rates. The same rank order was evident in 1998. The rate for American Indian or Alaska Natives increased by 28 percent from 19.6 to 25.1 per 100,000. The lung cancer death rate for Hispanics declined by 13 percent, the rate for black non-Hispanics declined by 10 percent, the rate for white non-Hispanics declined by 4 percent, and the rate for Asian or Pacific Islanders declined by 2 percent. The decline for Asian or Pacific Islanders was not statistically significant.

In 1990 the highest rate (50.9 per 100,000 for black non-Hispanics) was 3.2 times the lowest rate (15.7 per 100,000 for Hispanics). In 1998 the highest rate (46 per 100,000 for black non-Hispanics) was 3.4 times the lowest rate (13.6 per 100,000 for Hispanics). The relative difference between highest and lowest rates had increased slightly.

From 1990 to 1998 the age-adjusted lung cancer death rate for the total population declined by 7 percent from 39.8 to 37.0 per 100,000. The lung cancer death rate for black non-Hispanics declined by 10 percent, which is consistent with the aim of the special population target for black males in Objective 3.2.

Female breast cancer death rate

Between 1990 and 1998, the age-adjusted female breast cancer death rate for white non-Hispanics declined by 19 percent, the rate for Hispanics declined by 14 percent, and the rate for black non-Hispanics declined by 4 percent (table 1). Despite intervening fluctuations, the rate for Asian or Pacific Islanders was nearly unchanged and the rate for American Indian or Alaska Natives increased by 4 percent. Neither of these changes was statistically significant.

The age-adjusted female breast cancer death rate for black non-Hispanics was 2.8 times the rate for Asian or Pacific Islanders in 1990. The rate for black non-Hispanics declined by 4 percent and the rate for Asian or Pacific Islanders declined by 1 percent. In 1998 the ratio of the rates for these two groups was 2.7.

Despite the fact that there was a special population target for breast cancer death rates among black females, the rate for non-Hispanic black females declined by only 4 percent while the rate for the total population declined by 18 percent from 23.0 per 100,000 in 1990 to 18.8 per 100,000 in 1998.

Motor vehicle crash death rate

The age-adjusted motor vehicle crash death rate for Asian or Pacific Islanders declined by 31 percent from 1990 to 1998, the rates for Hispanics declined by 22 percent, and the rates for white non-Hispanics declined by 13 percent (table 1). The rates for black non-Hispanics declined by 6 percent and the rates for American Indian or Alaska Natives declined by 4 percent; the latter decline was not statistically significant. The group with the highest rate in 1990 (American Indian or Alaska Native) declined the least; the group with the lowest rate in 1990 (Asian or Pacific Islander) declined the most.

In 1990 the ratio of the rate for the highest group (American Indian or Alaska Native) to the rate for the lowest group (Asian or Pacific Islander) was 2.6. In 1998 the ratio of the rate for the highest group to the lowest group was 3.7. The relative difference between the highest and lowest groups increased during this period.

Suicide death rate

During the first half of the decade there were increases in age-adjusted suicide death rates for all groups except for white non-Hispanics (data not shown). Comparing rates in 1990 with those in 1998, rates declined by 17 percent for Hispanics, by 13 percent for black non-Hispanics, by 6 percent for white non-Hispanics, and by 2 percent for Asian or Pacific Islanders (table 1). The decline in suicide rates for Asian or Pacific Islanders was not statistically significant. The age-adjusted suicide death rate for American Indian or Alaska Natives increased by 8 percent from 1990 to 1998; however, this increase was not statistically significant. While black non-Hispanics, Hispanics, and Asian or Pacific Islanders had nearly the same rate in 1998, substantial differences in rates remain between these groups and the white non-Hispanic and American Indian or Alaska Native groups.

In 1990 white non-Hispanics had the highest age-adjusted suicide death rate, which was 2.1 times the lowest rate. In 1998 American Indian or Alaska Natives had the highest rate, which was 2.3 times the lowest rate.

Despite the fact that there was a special population target for American Indian or Alaska Native males, the age-adjusted suicide death rate for American Indian or Alaska Natives increased by 8 percent while the rate for the total population decreased by 10 percent.

Homicide death rate

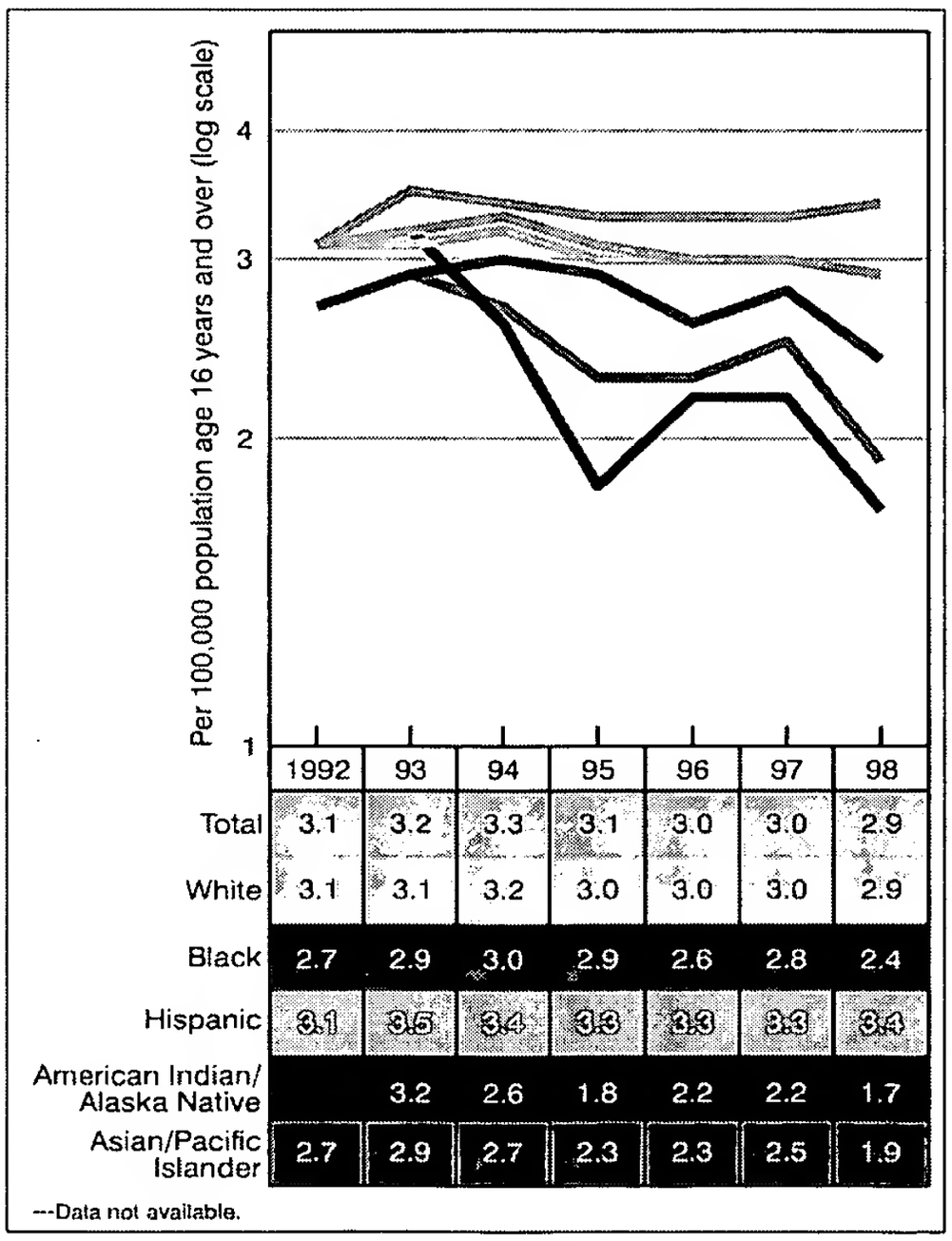
During the period from 1990 to 1998 the age-adjusted homicide death rate declined by 43 percent for Hispanics, by 34 percent for black non-Hispanics, by 29 percent for Asian or Pacific Islanders, by 22 percent for white non-Hispanics, and by 11 percent for American Indian or Alaska Natives (table 1). The decline for American Indian or Alaska Natives was not statistically significant.

In 1990 the age-adjusted homicide death rate for black non-Hispanics was 9.7 times the rate for white non-Hispanics. In 1998 the rate for black non-Hispanics was 8.2 times the rate for white non-Hispanics.

The homicide death rate for the total population declined by 28 percent from 10.2 per 100,000 in 1990 to 7.3 per 100,000 in 1998. Greater percent declines for Hispanics and for black non-Hispanics are consistent with special population targets for these groups; however, the smaller decline in rates for American Indian or Alaska Natives was contrary to the intent of the special population target for this group in Objective 7.1.

Work-related injury death rate

Work-related injury deaths are relatively rare events, occurring on the order of about 3 per 100,000 persons 16 years of age and over. The rates by race/ethnicity are shown in figure 5. In these data whites and blacks include persons of Hispanic origin. In 1992, the first year for which data from the Census of Fatal Occupational Injuries (CFOI) is available, rates ranged from 2.7 for blacks and Asian or Pacific Islanders to 3.1 for whites and Hispanics. Data for American Indians or Alaska Natives are not available for 1992. Between 1993 and 1998, rates declined by 47 percent for American Indian or Alaska Natives, by 34 percent for Asian or Pacific Islanders, by 17 percent for blacks, by



	1992	93	94	95	96	97	98
Total	3.1	3.2	3.3	3.1	3.0	3.0	2.9
White	3.1	3.1	3.2	3.0	3.0	3.0	2.9
Black	2.7	2.9	3.0	2.9	2.6	2.8	2.4
Hispanic	3.1	3.5	3.4	3.3	3.3	3.3	3.4
American Indian/ Alaska Native		3.2	2.6	1.8	2.2	2.2	1.7
Asian/Pacific Islander	2.7	2.9	2.7	2.3	2.3	2.5	1.9

---Data not available.

Figure 5. Work-related injury death rates by race and Hispanic origin: United States, 1992–98

6 percent for whites, and by 3 percent for Hispanics. The statistical significance of changes in work-related injury death rates was not assessed.

The ratio of the highest race/ethnic-specific rate to the lowest race/ethnic-specific rate was 1.1 in 1992 and 2 in 1998. A distinct divergence in rates is evident in figure 5.

Tuberculosis case rate

Tuberculosis case rates for Asian or Pacific Islanders declined more slowly than case rates for the other groups as indicated by the slope of the lines in figure 6. The tuberculosis case rate for Asian or Pacific Islanders declined by 15 percent from 1990 to 1998. The rate for white non-Hispanics, the group with the lowest rate in 1990, declined by 45 percent. The rates for black non-Hispanics declined by 46 percent; and the rates for Hispanics and for American Indian or Alaska Natives declined by 37 percent. The statistical significance of changes in tuberculosis case rates was not assessed.

The tuberculosis case rate for Asian or Pacific Islanders in 1990 was more than 10 times the rate for white non-Hispanics. In 1998 the rate for Asian or Pacific Islanders was more than 15 times the rate for white non-Hispanics. A widening of the gap between the highest and lowest rates is evident in figure 6.

The tuberculosis case rate for the total population declined by 34 percent from 10.3 to 6.8 per 100,000. The tuberculosis case rates for black non-Hispanics, American Indian or Alaska Natives, and for Hispanics declined by greater percents (46 percent, 37 percent, and 37 percent, respectively) consistent with special population targets for these groups. The tuberculosis case rate for Asian or Pacific Islanders, the group with the highest rates, declined the least (15 percent). This decline was inconsistent with the intent of the special population target for Asian or Pacific Islanders in Objective 20.4.

Primary and secondary syphilis case rate

The two groups with the highest rates of syphilis in 1990, black non-Hispanics and Hispanics, had the greatest declines (88 percent and 90 percent, respectively) (figure 7). The two groups with the lowest rates of syphilis in 1990, white non-Hispanics and Asian or Pacific Islanders, declined by smaller proportions (81 percent and 73 percent, respectively). The syphilis case rates declined the least for American Indian or Alaska Natives (49 percent). The statistical significance of changes in primary and secondary syphilis case rates was not assessed.

In 1990 the primary and secondary syphilis case rate for black non-Hispanics (141.9 per 100,000) was 95 times the rate for Asian or Pacific Islanders (1.5). In 1998 the rate for black non-Hispanics (16.9) was 42 times the rate for Asian or Pacific Islanders (0.4).

The Healthy People 2000 target for Objective 19.3 for the total population (4.0 per 100,000) was attained in 1997 (3.2 per 100,000) and the special population target for blacks (30.0 per 100,000) was attained in 1996. Between 1990 and

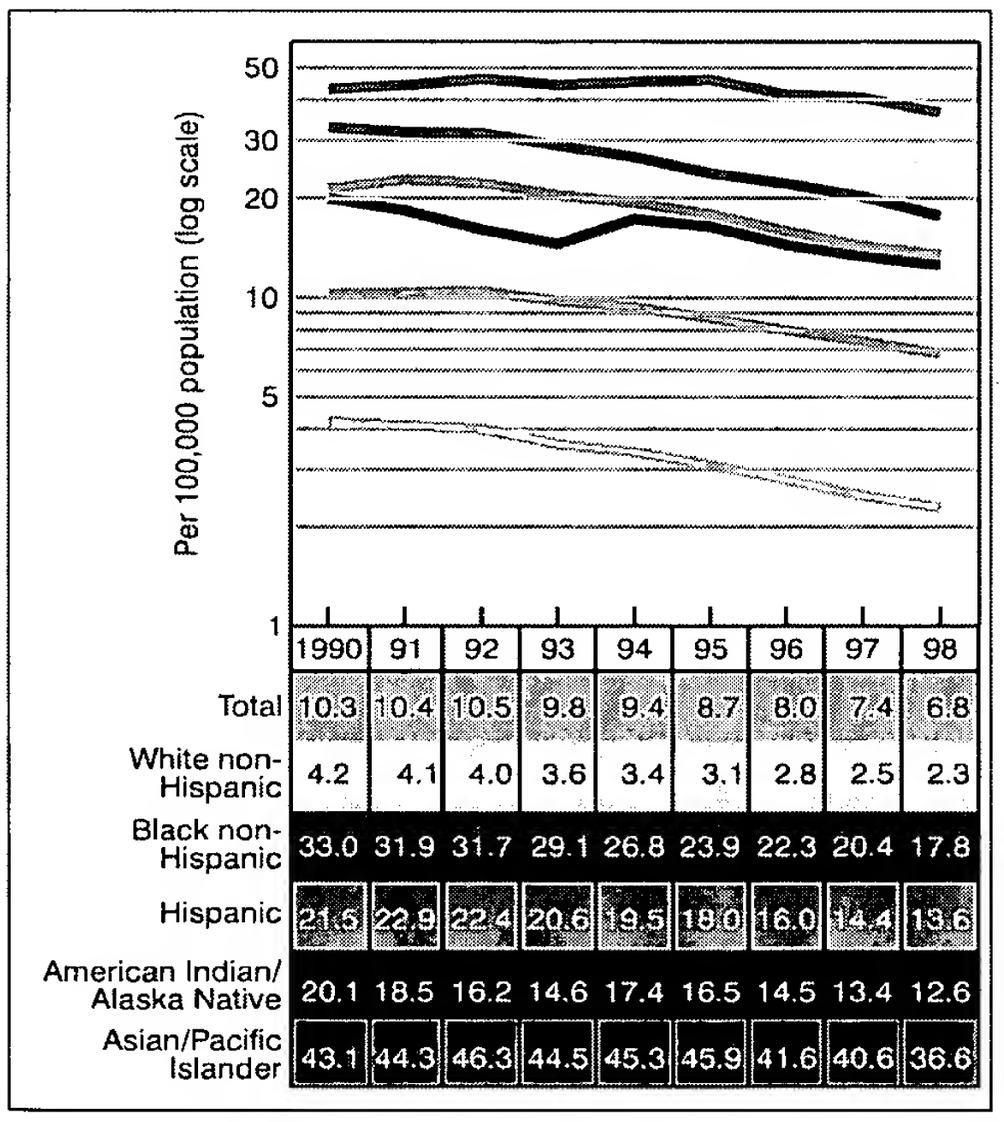


Figure 6. Tuberculosis case rates by race and Hispanic origin: United States, 1990–98

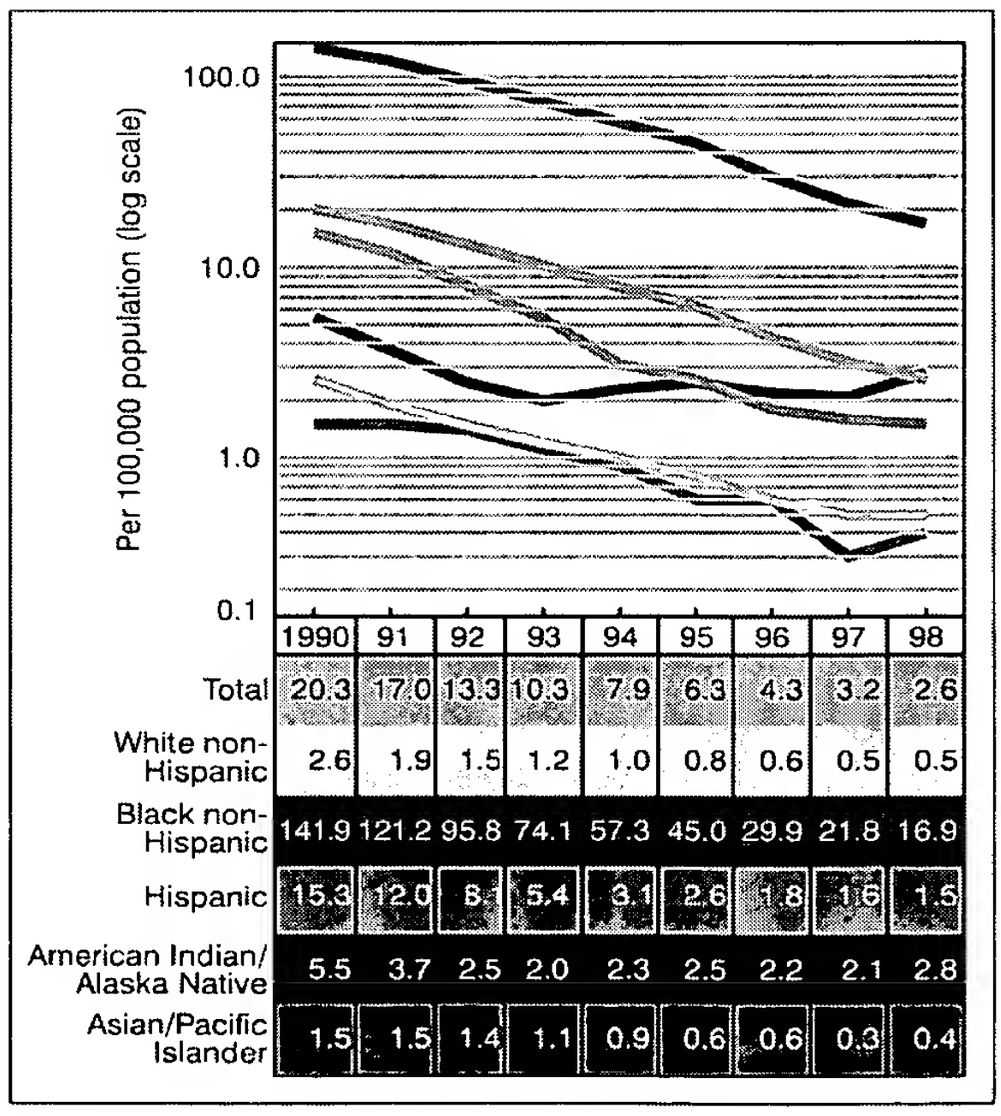


Figure 7. Primary and secondary syphilis case rates by race and Hispanic origin: United States, 1990–98

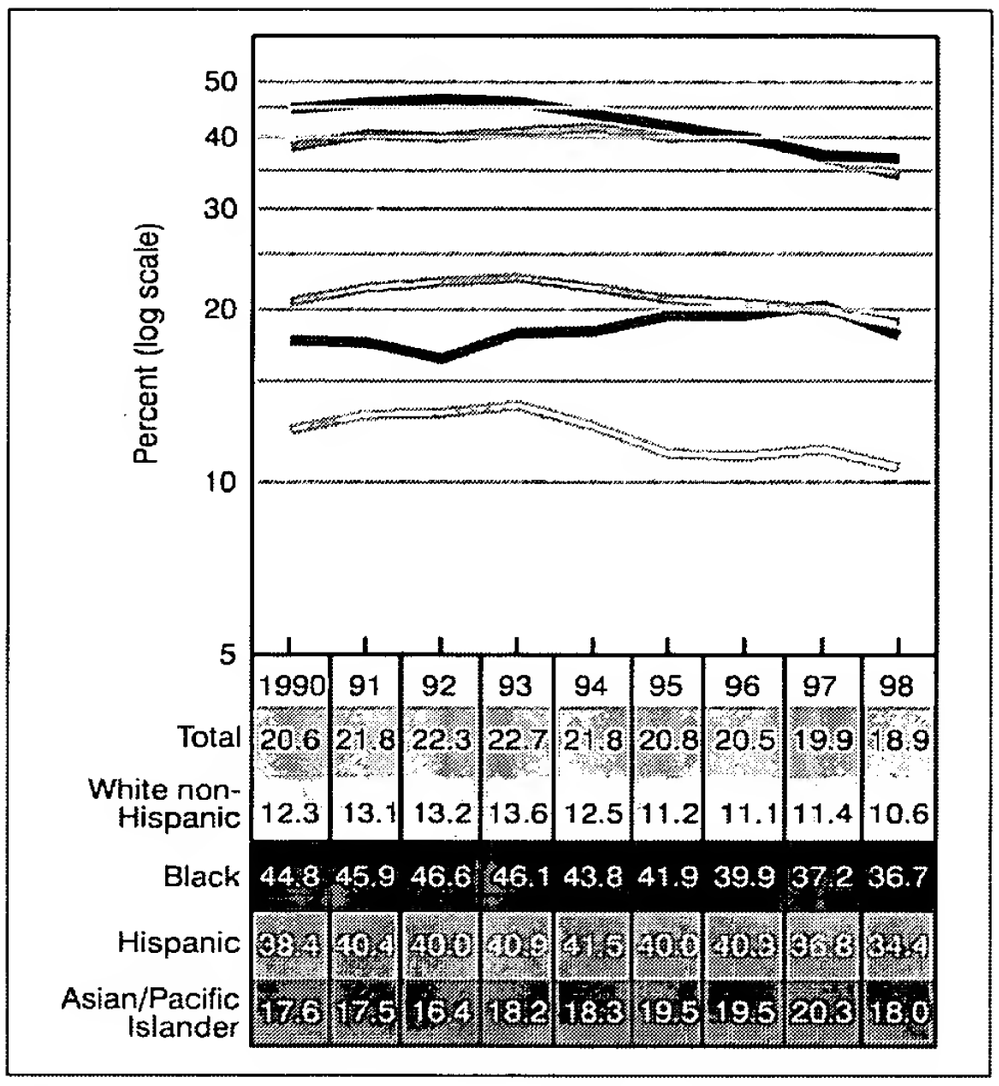


Figure 8. Percent of children under 18 years old in poverty by race and Hispanic origin: United States, 1990–98

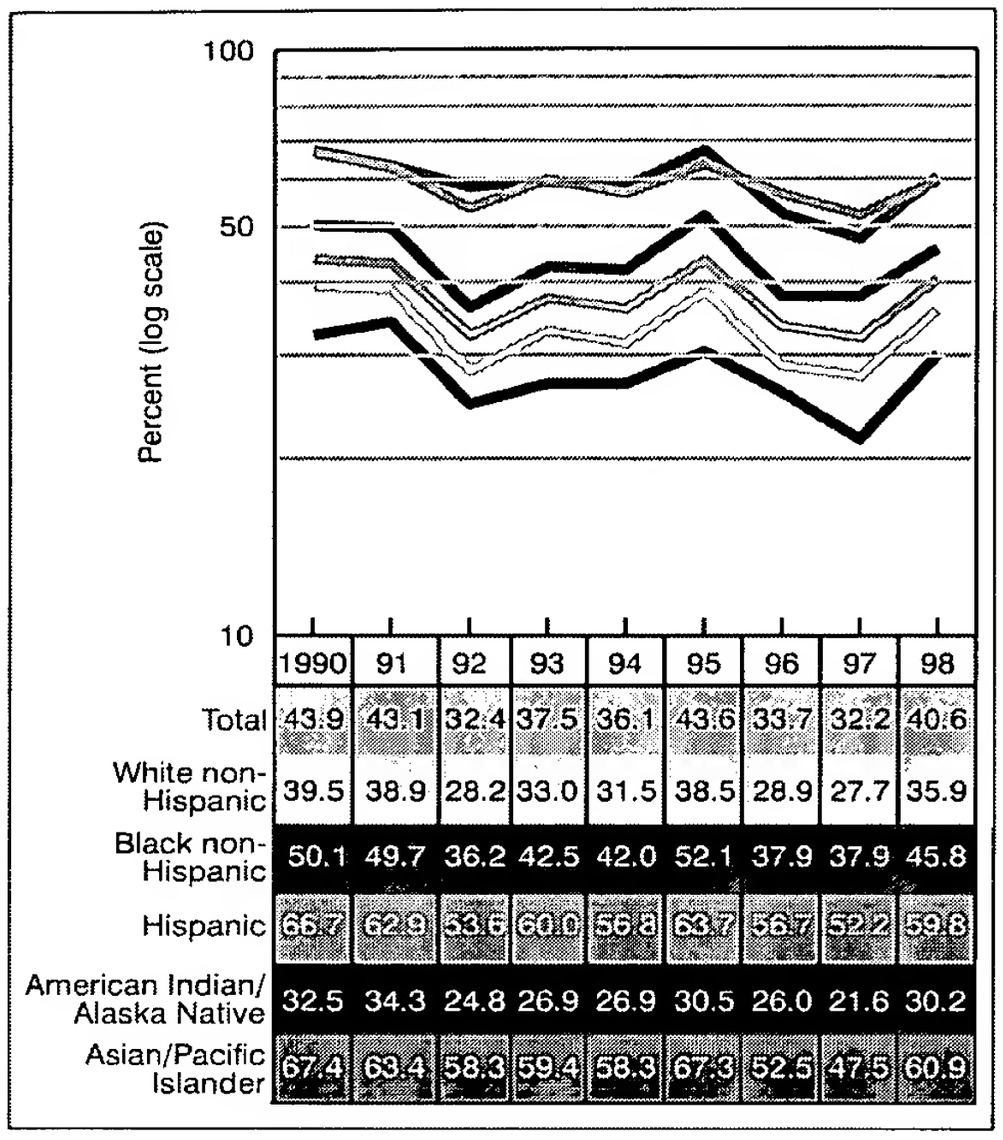


Figure 9. Percent of persons in counties exceeding EPA standards for air quality by race and Hispanic origin: United States, 1990–98

1998 the primary and secondary syphilis case rate declined by 87 percent for the total population, from 20.3 per 100,000 in 1990 to 2.6 per 100,000 in 1998, while the rate for black non-Hispanics declined by 88 percent. The percent change for the special population was, therefore, greater than the percent change for the total population.

Percent of children under 18 years old in poverty

After 1990 the percent of children under age 18 years living in poverty increased among white non-Hispanics until 1993, among blacks until 1992, among Hispanics until 1994 and among Asian or Pacific Islanders until 1997 (figure 8). Subsequent declines were evident for all racial/ethnic groups. Between 1990 and 1998 the percent of children under 18 in poverty declined by 18 percent for blacks, by 14 percent for white non-Hispanics, and by 10 percent for Hispanics. Between 1990 and 1998 the percent of children under age 18 years in poverty increased by 2 percent for Asian or Pacific Islanders. The increase for Asian or Pacific Islanders was not statistically significant.

In 1990 the poverty rate for black children under 18 years of age, the highest group, was 3.6 times the rate for white non-Hispanic children. In 1998 the rate for black children was 3.5 times the rate for white non-Hispanic children.

Percent of persons in counties exceeding EPA air quality standards

Weather patterns have a substantial impact on air quality and the cyclical nature of these patterns is evident in figure 9 (7). The percent of persons in counties exceeding EPA standards for air quality declined for all racial/ethnic groups from 1990 to 1992, then increased for all groups from 1992 to 1995. The percent of persons in counties exceeding EPA air quality standards declined again from 1995 to 1997, and increased again between 1997 and 1998. Either Hispanics or Asian or Pacific Islanders had the highest percent of persons in counties exceeding EPA air quality standards each year between 1990 and 1998. The other three racial/ethnic groups maintained their same relative positions throughout the period. American Indian or Alaska Natives had the lowest percent of persons in counties exceeding EPA air quality standards, followed by white non-Hispanics and black non-Hispanics. Given the cyclic nature of this indicator, comparisons between 1990 and 1998 are not very meaningful.

The ratio between the group with the highest percent of persons in counties exceeding EPA air quality standards and the group with the lowest percent of persons in such counties was 2.1 in 1990, 1.8 in 1991, 2.4 in 1992 and 1997, 2.2 in 1993–96, and 2.0 in 1998. The relative difference between the group with the highest percent and the group with the lowest percent was rather consistent during this period.

Comparing a summary measure of disparity for 1990 and 1998

The index of disparity summarizes the differences among group rates. This statistic provides a basis for

Table 2. Index of disparity among five racial/ethnic groups for the Health Status Indicators: United States, 1990, 1998, and percent change

	Index of disparity		Percent change 1990–98	
	1990	1998	Decrease	Increase
Infant mortality rates	38.9	36.4	–6.4	
Low birthweight (percent)	28.4	23.0	–19.0**	
No prenatal care in first trimester (percent)	46.9	43.5	–7.2**	
Live birth rates for women age 15–17 years	65.4	67.7		3.5**
Total death rates	27.9	25.8	–7.5**	
Heart disease death rates	31.1	30.9	–0.6	
Stroke death rates	29.6	26.4	–10.8**	
Lung cancer death rates	39.0	35.4	–9.2**	
Female breast cancer death rates	34.3	33.6	–2.0	
Motor vehicle crash death rates	23.6	32.8		39.0**
Suicide death rates	28.2	33.8		19.9**
Homicide death rates	95.5	86.8	–9.1**	
Work-related injury death rates (1993–98)[1]	6.3	22.1		250.8[a]
Tuberculosis case rates	160.4	170.3		6.2[a]
Primary and secondary syphilis case rates	175.3	153.1	–12.7[a]	
Children under age 18 years in poverty (percent)[2]	64.7	56.2	–13.1	
Percent with poor air quality (1992–1998)	31.1	29.5	–5.1[a]	

**The difference in the index of disparity is statistically significant at the 0.05 level.

[a]The statistical significance of the difference in the index of disparity was not tested. Methods for assessing the reliability of the underlying rates are not available.

[1]The index of disparity for work-related injury deaths is not strictly comparable with the index of disparity for the other indicators because the data are available for the following groups: white, black, Hispanic, American Indian, Aleut and Eskimo, and Asian or Pacific Islanders. Persons of Hispanic origin may be of any race.

[2]The index of disparity for the percent of children in poverty is not strictly comparable with the index of disparity for the other indicators because the data are available for the following groups: white non-Hispanic, black, Hispanic, and Asian or Pacific Islander.

comparing the degree of difference (disparity) in race/ethnic specific rates in 1990 with the disparity in race/ethnic rates in 1998. The index of disparity was calculated for each of the HSIs in 1990 and in 1998 and the percent change in the index of disparity between 1990 and 1998 was calculated (table 2). The index of disparity for infant mortality rates by race and Hispanic origin was 38.9 percent in 1990. This statistic indicates that the disparity among racial/ethnic groups was equal to 38.9 percent of the total infant mortality rate. In 1998 the disparity among racial/ethnic groups was equal to 36.4 percent. A decline in the index of disparity indicates that the disparity in race/ethnic specific rates declined relative to the total rate. The index of disparity for the infant mortality rate declined by 6.4 percent between 1990 and 1998; this difference was not statistically significant.

The index of disparity declined for 12 of the 17 HSIs. Declines in the index of disparity were statistically significant for six of the HSIs: Percent of low birthweight infants (–19 percent), percent of women with no prenatal care in the first trimester (–7.2 percent), total death rate (–7.5 percent), stroke death rate (–10.8 percent), lung cancer death rate (–9.2 percent), and the homicide death rate (–9.1 percent). Declines in the index of disparity were not statistically significant for the infant mortality rate, heart disease death rate, female breast cancer death rate, and percent of children under age 18 in poverty. The significance of changes in the index of disparity for the syphilis case rate and for the percent of persons with poor air quality could not be assessed.

The index of disparity increased for the other five HSIs. Increases in the index of disparity were statistically significant for three HSIs: The live birth rate for women age 15–17 years (+3.5 percent), motor vehicle crash death rate (+39.0 percent), and the suicide death rate (+19.9 percent). The statistical significance of increases in the index of disparity for the work-related injury death rate (+250.8) and the tuberculosis case rate (+6.2) could not be assessed. An increase in the index of disparity can be interpreted as an increase in the racial/ethnic disparity among rates.

Comparing racial and ethnic disparity among the HSIs

The index of disparity also provides a basis for comparing the degree of racial/ethnic disparity among indicators (table 3). Tuberculosis case rates had the highest index of disparity in 1998 (170.3 percent). Primary and secondary syphilis case rates had the second highest index of disparity (153.1 percent) followed by homicide death rates (86.8 percent), and live birth rates to women age 15–17 years (67.7 percent). These four indicators also had the greatest ratios of highest to lowest race/ethnic-specific rates in 1998 (42 for syphilis, 16 for tuberculosis, 8 for homicide, and 4.5 for live birth rates to women age 15–17). The magnitude of the index value for primary and secondary syphilis case rates is primarily a function of the extraordinarily high rate for black non-Hispanics (figure 7). The magnitude of the index values for tuberculosis case rates, homicide death rates, and live birth rates for women age 15–17 are a function of substantial differences between the overall population rate (dominated by the white non-Hispanic group) and the other four racial/ethnic groups (figure 6, table 1, and figure 4, respectively).

Table 3. Index of disparity among five racial/ethnic groups for the Health Status Indicators: United States, 1998

	Index of disparity 1998
Tuberculosis case rates	170.3
Primary and secondary syphilis case rates	153.1
Homicide death rates	86.8
Live birth rates for women age 15–17 years	67.7
Children under age 18 years in poverty (percent)[1]	56.2
No prenatal care in first trimester (percent)	43.5
Infant mortality rates	36.4
Lung cancer death rates	35.4
Suicide death rates	33.8
Female breast cancer death rates	33.6
Motor vehicle crash death rates	32.8
Heart disease death rates	30.9
Percent with poor air quality (1992–98)	29.5
Stroke death rates	26.4
Total death rates	25.8
Low birthweight (percent)	23.0
Work-related injury death rates (1993–98)[2]	22.1

[1]The index of disparity for the percent of children in poverty is not strictly comparable with the index of disparity for the other indicators because the data are available for the following groups: white non-Hispanic, black, Hispanic, and Asian or Pacific Islander.
[2]The index of disparity for work-related injury deaths is not strictly comparable with the index of disparity for the other indicators because the data are available for the following groups: white, black, Hispanic, American Indian, Aleut and Eskimo, and Asian or Pacific Islanders. Persons of Hispanic origin may be of any race.

Despite the fact that the index of disparity for work-related injury deaths increased by 250.8 percent between 1990 and 1998, work-related injury deaths had the smallest index of disparity in 1998 (22.1 percent). While differences in work-related injury death rates have increased since the data first became available, the relative size of differences remains small. The ratio of highest to lowest race/ethnic-specific work-related injury death rates was 2 in 1998. The remaining indicators had indexes of disparity ranging from 23 to 56 percent.

Conclusions

Trends in the HSIs

An earlier report noted that substantial improvements were made in the HSIs for the total population (8). National targets for the Healthy People 2000 objectives that correspond to the HSIs have been attained for six of the indicators and the United States had significantly improving trends for 14 indicators. No significant improvement was evident for lung cancer deaths, work-related injury deaths, and homicide deaths; and the percent of low birthweight infants was increasing significantly instead of decreasing.

Trends in race/ethnic-specific rates were examined in this report for 17 HSIs. All five racial/ethnic groups experienced at least nominal reductions in rates for 10 of the HSIs between 1990 and 1998: heart disease death rates, motor vehicle crash death rates, work-related injury death rates (between 1993 and 1998), homicide death rates, tuberculosis case rates, primary and secondary syphilis case rates, infant mortality rates, percent of women with no prenatal care in the first trimester, live birth rates for women age 15–17 years, and percent of persons in counties exceeding EPA air quality standards.

For four additional HSIs, there was at least nominal improvement between 1990 and 1998 in rates for all groups except American Indian or Alaska Natives: total death rates, stroke death rates, lung cancer death rates, and suicide death rates. Female breast cancer death rates declined at least nominally for white non-Hispanics, black non-Hispanics, and Hispanics; increased for American Indian or Alaska Natives; and were unchanged for Asian or Pacific Islanders. The percent of low birthweight increased for all racial/ethnic groups except for black non-Hispanics. The percent of children under 18 years old in poverty increased only for Asian or Pacific Islanders.

The findings concerning American Indian and Alaska Natives stood out for six of the HSIs. Between 1990 and 1998, the lung cancer death rate for American Indian or Alaska Natives increased by 28 percent, the percent of low birthweight infants increased by 11 percent, the suicide death rate increased by 8 percent, the total death rate and the breast cancer death rate each increased by 4 percent, and the stroke death rate increased by 3 percent. While the changes in the suicide, breast cancer, and stroke death rates were not statistically significant, American Indian or Alaska Natives do not appear to have experienced the same improvements in these indicators as the other racial/ethnic groups experienced. While there may be alternative explanations for these findings, such as improvement in the identification of native peoples during this period, further investigation is needed.

Special population targets

Ten of the HSIs correspond to Healthy People 2000 objectives with special population targets intended to reduce differences in rates between a specific racial/ethnic group and the total population. The special population target for syphilis case rates among blacks was attained. Declines in stroke death rates, lung cancer death rates, homicide death rates, tuberculosis case rates, and in the percent of women with no prenatal care during the first trimester were greater for black non-Hispanics than they were for the total population. These reductions were consistent with the goal of reducing disparities. Declines for black non-Hispanics were not greater than declines for the total population in female breast cancer death rates or in infant mortality rates despite special population targets. There was no decline in the percent of low birthweight infants for black non-Hispanics despite a special population target for blacks.

Compared with changes for the total population, Hispanics experienced greater declines in homicide death rates and tuberculosis case rates. These changes were consistent with special population targets intended to produce greater improvements for Hispanics.

Among American Indian or Alaska Natives, changes in suicide and homicide death rates were in the opposite direction of that intended by special population targets for Objectives 6.1 and 7.1. On the other hand, tuberculosis case

rates and infant mortality rates declined by greater percents for American Indian or Alaska Natives compared with the total population. These changes were consistent with the intent of special population targets for these objectives.

The tuberculosis case rate for Asian and Pacific Islanders was the highest of the five racial/ethnic groups and declined the least, despite the fact that there was a special population target for tuberculosis case rates for this group (Objective 20.4).

The index of disparity

Examination of the race/ethnic-specific rates for the HSIs indicates that substantial disparities in rates persist. The comparison of percent changes in rates over time provides a good indication of which groups are not improving and which groups are improving by greater margins. The ratio comparisons are indicative of relative changes between groups with the highest and lowest rates but they do not provide information about how the rates for the groups in between are changing. These comparisons do not lend themselves to a summary conclusion about how differences among all five groups are changing for a particular indicator. In order to draw such conclusions, an index of disparity was employed as a summary measure of differences in race/ethnic specific rates. The index of disparity is employed to measure changes in disparity over time and to compare the degree of disparity among indicators.

The index of disparity provides a measure of variability in race/ethnic specific rates relative to the rate for the total population. The index of disparity decreased for 12 HSIs. The index of disparity for the percent of low birthweight infants decreased by 19 percent; however, this decrease was the result of increases in rates for the four racial/ethnic groups with the lowest rates at the beginning of the period. The index of disparity decreased by less than 10 percent for nine of the HSIs.

Increases in the index of disparity for motor vehicle crash death rates, work-related injury death rates, suicide death rates, and tuberculosis case rates were due to the divergence in racial/ethnic rates. In each of these instances, the racial/ethnic group with the highest rate in 1990 had little or no decline from 1990 to 1998 (see table 1 and figures 5 and 6).

The index of disparity also provides a basis for comparing the disparity in rates among indicators. The HSIs with the highest index values are tuberculosis case rates, syphilis case rates, homicide death rates, live birth rates for women age 15–17 years, and percent of children under age 18 in poverty.

Implications of this study

While the validity of the findings presented here depends upon the accuracy of the reporting of race and ethnicity, it is not likely that all of the differences observed here are the result of errors in reporting or changes in reporting of race and ethnicity over time.

One of the overarching goals of Healthy People 2000 was to reduce—and finally eliminate—disparities among population groups of Americans (2). In pursuit of this goal special population targets were established where specific sex, race, ethnic, age, income, or education groups were known to have less favorable rates. In Healthy People 2010 the overarching goal is to "eliminate health disparities among different segments of the population"(9). These include differences that occur by gender, race or ethnicity, education or income, disability, living in rural localities, or sexual orientation. In Healthy People 2010, the objectives will be monitored for as many of these characteristics as possible. Based on this analysis relatively little progress was made toward the goal of eliminating racial/ethnic disparities among the HSIs during the last 10 years. Progress toward the goal of eliminating health disparities will require more concerted efforts during the next 10 years.

Methods

The Health Status Indicators (HSIs)

Committee 22.1 designated 18 HSIs (1). The HSIs are based on established data collection systems with standardized definitions and collection procedures (10). The indicator for cardiovascular disease deaths included two subcategories, heart disease and stroke. Because the trends in these subcategories are distinguishable, the findings are presented for the two subcategories. Reported cases of AIDS were included as one of the original HSIs. Since the case definition for AIDS changed in 1993 and because the transition from HIV infection to AIDS has been altered substantially by the introduction of drug therapies, the original measure is not a reliable indicator of trends during the 1990s or a valid indicator of HIV infection. Therefore, reported cases of AIDS are not examined here. Reported cases of measles were also one of the original HSIs. Until recently the proportion of measles cases with race "not stated" was too large to permit valid calculation of race-specific case rates and the number of measles cases is now small enough to make the calculation of race/ethnic specific rates impractical. As a result, reported cases of measles are also not examined in this report.

The proportion of live births to adolescents (ages 10–17) was one of the original HSIs. This indicator is easily measured from birth certificate data; however, the proportion of births to adolescents is not an adequate basis for comparing teenage fertility among different populations. The proportion of all births to adolescents is also a function of the fertility of older women. The live birth rate for teenagers 15–17 years is a much better measure of teenage fertility for comparative purposes. The birth rate is calculated by dividing the number of live births to women age 15–17 years in a calendar year by the population of females age 15–17 at the midpoint of that calendar year. The result is multiplied by 1,000 and the result is expressed as a birth rate per 1,000 females age 15–17 years of age. Omitting AIDS

and measles and subdividing cardiovascular disease into two indicators, this report presents findings for 17 indicators.

Race and Hispanic origin

The HSIs are based on a variety of data collection systems with different data collection procedures. Generally these data systems record the subject's race in terms of white, black, American Indian or Alaska Native, and Asian or Pacific Islander; and the subject's origin in terms of Hispanic or non-Hispanic. These two measures of race and ethnicity are combined to form five groups (white non-Hispanic, black non-Hispanic, Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander). Persons of Hispanic origin can be of any race. While the categories white non-Hispanic and black non-Hispanic exclude persons reported as Hispanic, small numbers of Hispanics are included among the American Indian or Alaska Native and Asian or Pacific Islander groups. Whenever possible, the rates and percents for the HSIs were calculated for each of these five groups. Work-related injury deaths are tabulated according to white, black, Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander (11). Since Hispanics may be of any race, they are also included among the other four groups. The percent of children under 18 years old in poverty is tabulated for the following four categories: white non-Hispanic, black, Hispanic, and Asian or Pacific Islander. Hispanics are included among the black and Asian or Pacific Islander groups.

The validity of the findings in this report depends upon the accuracy of race and ethnic data. A number of studies have been conducted on the reliability of race reported on the death certificate by comparing race on the death certificate with that reported on another data collection instrument, such as the census or a survey. Differences may arise because of differences in who provides race information on the compared records. Race information on the death certificate is reported by the funeral director as provided by an informant or, in the absence of an informant, on the basis of observation. In contrast, race on the census is obtained while the individual is alive and is self-reported or reported by another member of the household. Studies (12, 13) show that a person self-reported as American Indian or Asian on census or survey records was sometimes reported as white on the death certificate. The net effect of misclassification is an underestimation of deaths and death rates for races other than white and black. In addition, undercoverage of minority groups in the census and resultant population estimates introduces biases into death rates by race (6). Estimates of the approximate effect of the combined bias due to race misclassification on death certificates and under enumeration on the 1990 census are as follows: white, –1.0 percent; black, –5.0 percent; American Indian, +20.6 percent; and Asian or Pacific Islander, +10.7 percent. Death rates for the Hispanic population are also affected by undercoverage of this population group in the census and resultant population estimates; the estimated net correction, taking into account both sources of bias is +1.6 percent. The extent to which racial and ethnic misclassification may have changed from 1990 to 1998 is unknown.

Misclassification is less of a problem for information from birth certificates to the extent that information is supplied by an informant and proportions or rates are calculated based solely on information from the birth certificate. In the linked birth-infant death file, the mother's race on the birth certificate is used for purposes of computing infant mortality rates. The effects of misclassification on the comparisons made here cannot be estimated.

Rates and percents

The HSIs are based on rates or percents that permit comparisons among populations or geographic areas with populations of different size. The death rates are age adjusted to the 1940 standard population to eliminate the effects of differences in age composition from comparisons among populations (14). These rates represent the number of deaths that would occur per 100,000 persons if the standard population had the age-specific death rates of the population of interest. It should be remembered that these age-adjusted rates are appropriate for comparison purposes and that they have no inherent meaning for most other purposes.

Age-specific population data for the calculation of rates by race and ethnicity were extracted from Census Bureau estimates for the year 1998 along with corresponding adjustments in estimates going back to 1990: U.S. Census Bureau; http://www.census.gov/population/www/estimates/expectancyst_sasrh.html (revised September 15, 1999).

The trends in race/ethnic-specific rates and percents for each HSI are shown in tables and graphs. When graphs are shown, the vertical axis for the rates and percents is shown on a log scale. The log scale provides for a visual comparison of the proportional change in rates over time. In this case the change for each of the five racial/ethnic groups can be compared directly. The log scale compensates for differences in the level of an indicator among groups. On the normal scale, a change from 50 percent to 45 percent (a reduction of 10 percent) appears to be as great as a change from 10 percent to 5 percent (a reduction of 50 percent). On the log scale a change from 50 percent to 25 percent (a 50 percent reduction) would appear as great as a change from 10 percent to 5 percent. When rates of change for two groups are compared on the log scale, proportional changes are indicated by parallel lines. Disproportional change between two groups is evident when the slopes of their trend lines are different. More steeply sloping lines are indicative of greater proportional changes.

The percent change in rates from the beginning of the period (usually 1990) to the end of the period (1998) are compared for the five race/ethnic specific groups. Unless otherwise noted, changes between 1990 and 1998 are statistically significant at the 0.05 level. Tests of significance were not conducted for tuberculosis case rates, syphilis case

rates, work-related injury death rates, and the percent of persons in counties exceeding EPA standards for air quality. The reporting of notifiable diseases, work-related injuries, and air quality are subject to errors in coverage that cannot be estimated routinely. The focus of the analysis is on the relative degree of change over time rather than on the statistical significance of the difference between initial and final rates. When the rates for two groups change by similar percents, there is no reduction in the relative difference between the rates for the two groups. When the rates for two groups change by different percents, the relative difference between the rates for the two groups is either increasing or decreasing.

The index of disparity

The discussion of differences in rates among groups becomes complicated when there are more than two groups. The index of disparity was developed as a summary measure of the differences between rates for subgroups in a population. The numerator of the index, the mean deviation, is obtained by first calculating the difference between each group rate and the rate for the total population. The absolute values of these differences are added and the sum is divided by the number of groups. The subgroup rates are not weighted according to the number of individuals in each group. The mean deviation would be suitable for comparisons among different sets of subgroups within a single population or between different populations with the same overall rate. The mean deviation is indicative of the degree of difference from the overall rate. It would not be appropriate to compare the mean deviation for a single indicator at two points in time when rates are changing or to compare the mean deviation between two indicators with different overall rates.

In order to make additional comparisons, the mean deviation is divided by the rate for the total population and multiplied by 100. Dividing by the total population rate standardizes the index. The degree of difference in the subgroup rates is expressed relative to the rate in the total population. Multiplying by 100 converts the ratio to a percent for convenience in making comparisons. The differences between the rates for the subgroups are, therefore, expressed as a percent of the total population rate. The resulting index of disparity can be used to compare differences in rates over time even if the overall rate in the population is changing. It can also be used to make comparisons among indicators with different means and to make comparisons among indicators with different metrics (i.e., percent; per 1,000; per 100,000, etc.).

The index of disparity also has certain limitations. It is a statistic that summarizes the differences between subgroup rates and the rate for the total population. It does not specify which group has the highest or lowest rate. It does not indicate how many groups are different from the total population or whether the differences in rates are statistically significant. Similar index values could be obtained when the rate for one group is very different from the total or when the rates for two groups are only moderately different from the total. When used to monitor changes in disparity over time, it does not tell us whether the overall rate in the population is increasing or decreasing. A decrease in the statistic does not necessarily indicate that the rate in the population is improving; it simply means that there is proportionally less difference in subgroup rates relative to the overall rate in the population. The index of disparity should be interpreted in conjunction with the race/ethnic-specific rates on which it is based.

A bootstrap procedure was employed to estimate a standard error for the index of disparity based on the underlying rates and their standard errors. The standard errors for the rates based on vital statistics data are estimates of nonsampling error since no sampling is involved in the collection of the data. The standard errors for the percents of children under 18 years old in poverty include both sampling and nonsampling error since they are estimates based on the Current Population Survey. The bootstrap procedure uses the rate and standard error for each group to produce 25,000 random numbers assuming a normal distribution. An estimate of the index of disparity is calculated from the generated rates. The distribution of the simulated index of disparity is used to derive an estimate of the standard error for the index. A z-test for the difference between two rates was used to determine whether changes in the index of disparity between 1990 and 1998 were statistically significant at the 0.05 level (15). A description of the methodology for calculating confidence limits for the index of disparity is available from the authors.

Sources of Data

Death rates (except work-related injury)

Numbers of deaths by race, Hispanic origin, cause of death, age, and in the case of breast cancer—for females only—were extracted from annual mortality files from the National Vital Statistics System. The cause-of-death categories were based on the following *International Classification of Diseases Ninth Revision* codes: total deaths (ICD–9 codes, all causes of death combined); heart disease deaths (ICD–9 codes 390–398, 402, and 404–429); stroke deaths (ICD–9 codes 430–438); lung cancer deaths (ICD–9 code 162.0); female breast cancer deaths (ICD–9 code 174); motor vehicle crash deaths (ICD–9 codes E810–E825); suicide deaths (ICD–9 codes E950–E959); and homicide deaths (ICD–9 codes E960–E978). In 1990, data for Louisiana, New Hampshire, and Oklahoma were excluded from this analysis of race/ethnic specific trends because Hispanic origin was not reported on the death certificate. Data for New Hampshire and Oklahoma were excluded in 1991 and 1992, and data for Oklahoma were excluded in 1993–96. In 1997 all States and the District of Columbia reported Hispanic origin on the death certificate. The data for each racial/ethnic group were extracted for 11 age groups so that age-adjusted rates could be computed. Age and race/ethnic-specific population denominator data were

extracted from Census Bureau estimates for the year 1998 along with corresponding adjustments in estimates going back to 1990: U.S. Census Bureau; http://www.census.gov/population/www/estimates/st_sasrh.html (revised September 15, 1999).

Work-related injury death rates

Data on injury-related deaths to workers 16 years of age and over for the years 1992–98 were drawn from the Census of Fatal Occupational Injuries (CFOI) database maintained by the Bureau of Labor Statistics. These data are reported for the following racial/ethnic categories: white, black, Hispanic, American Indian or Alaska Native, and Asian or Pacific Islander. The sources of annual population data cited previously were also employed as denominators here. The denominator was limited to the population 16 years of age and over.

Tuberculosis case rates

Tuberculosis case rates per 100,000 population by race/ethnicity from 1990 to 1998 were extracted from the following publications: Centers for Disease Control and Prevention, Reported Tuberculosis in the United States, 1998 (July 1999), 1997 (July 1998), 1996 (July 1997), 1995 (July 1996), 1994 (July 1995), 1993 (July 1994); and Tuberculosis Statistics in the United States 1990–92 (1994).

Syphilis case rates

Syphilis case rates per 100,000 population by race/ethnicity from 1990 to 1998 were provided by Emmett Swint, Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention.

Infant mortality rates

Numbers of live births and infant deaths according to the mother's race/ethnicity on the birth certificate were drawn from the annual linked birth/infant death data sets for the years 1990–92 and 1995–98. National linked files were not created for the years 1992–94.

Low birthweight and prenatal care

The percent of low birthweight infants was based on the number of live-born infants weighing less than 2,500 grams, divided by the total number of live-born infants according to the mother's race/ethnicity. Infants with no birthweight recorded were excluded from both the numerator and the denominator. The percent of women who did not begin prenatal care in the first trimester was based on the number of live births where the woman did not begin prenatal care during the first 3 months of pregnancy—including women who did not have any prenatal care. Live births for which the month care began was not stated were excluded from both the numerator and denominator. These frequencies were extracted from the annual natality files from the National Vital Statistics System.

Live birth rates for females age 15–17 years

These rates were based on the numbers of live births to women 15–17 years old by race/ethnicity extracted from the annual natality files from the National Vital Statistics System. The numbers of females 15–17 years old by State were supplied by Stephanie Ventura, Division of Vital Statistics, National Center for Health Statistics, based on previously published reports on birth rates for teenagers (16).

Percent of children under 18 years old in poverty

Data on the percent of children under 18 years old living in poverty by race/ethnicity were extracted from the following publication: U.S. Census Bureau, Poverty in the United States, 1998; Current Population Reports P60–207, September 1999. These data are reported for the following racial/ethnic categories: white non-Hispanic, black, Hispanic, and Asian and Pacific Islander.

Percent of persons in counties exceeding EPA standards for air quality

The Environmental Protection Agency (EPA) monitors the occurrence of air pollutants (carbon monoxide, nitrogen dioxide, ozone, lead, particulate matter, and sulfur dioxide) during the previous 12 months. Counties that did not meet EPA National Ambient Air Quality Standards (NAAQS) are identified in a database maintained by the Office of Air Quality Planning & Standards, Information Transfer & Program Integration Division, which can be found at: http://www.epa.gov/aqspubl1/select.html.

Counties where one or more of the six criteria pollutants exceeded NAAQS were tabulated by State and year. So-called "secondary exceedences" were used such that a county had to have at least two recorded values in excess of the NAAQS to be in exceedence. Any county with one or more secondary exceedences was considered in exceedence of the standards. Annual population estimates (as described above) for the counties that exceeded any standard were used to calculate the percent of persons living in counties exceeding EPA air quality standards for each racial/ethnic group. These methods differ from those used to monitor Healthy People 2000 Objective 11.5 and generally produce estimates of the percent of persons in counties exceeding EPA air quality standards higher than those for Objective 11.5.

When interpreting the results it is important to remember that the national network of air quality monitors is not uniformly distributed among counties and that many counties have no monitors at all. Also not accounted for in the data are effects of weather and climate on the concentration and distribution of pollutants in counties where monitors are located or adjacent counties which have no monitors.

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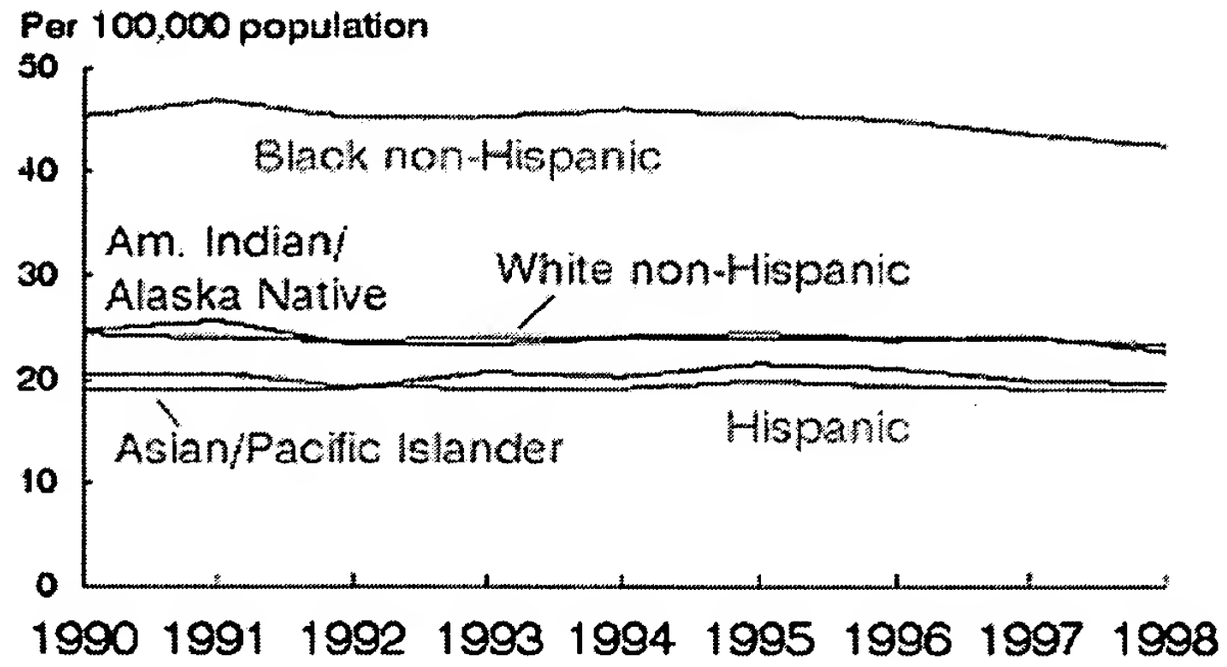
Stroke death rates (age adjusted to the year 1940 standard population)*



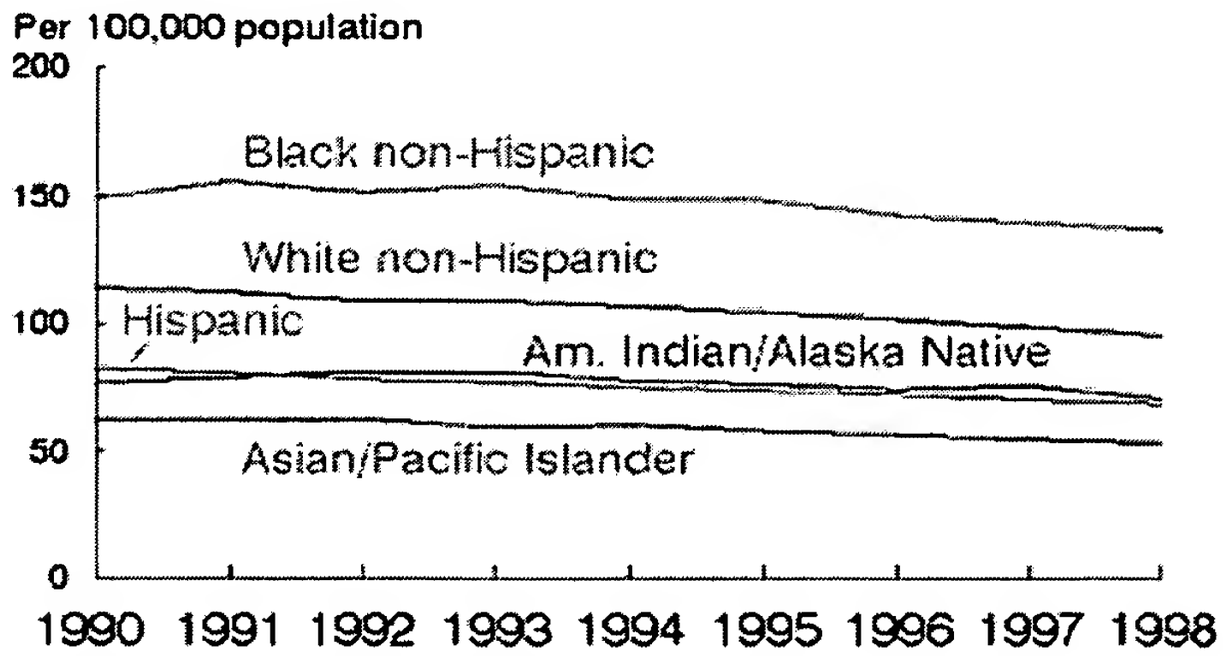
*Age adjustment to the year 2000 standard population will begin in 1999.
SOURCE: CDC/NCHS, National Vital Statistics System

Stroke death rates (age adjusted to the year 1940 standard population)*

	1990	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*
White non-Hispanic	24.4	24.0	23.6	24.0	24.1	24.3	24.0	23.9	23.3
Black non-Hispanic	45.4	46.9	45.2	45.3	46.0	45.6	44.9	43.6	42.5
Hispanic	20.5	20.6	19.3	19.2	19.2	19.9	19.4	19.2	19.0
Am. Indian/ Alaska Native	24.7	25.7	23.3	23.3	24.0	23.9	23.6	24.1	22.7
Asian/Pacific Islander	19.1	19.2	19.1	20.7	20.2	21.5	21.0	19.8	19.6

*Age adjustment to the year 2000 standard population will begin in 1999.
SOURCE: CDC/NCHS, National Vital Statistics System

Coronary heart disease death rates (age adjusted to the year 1940 standard population)*



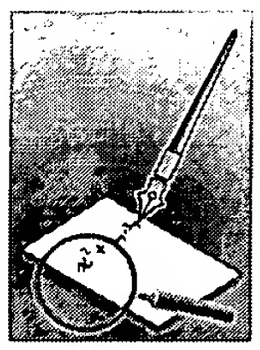
*Age adjustment to the year 2000 standard population will begin in 1999.
SOURCE: CDC/NCHS, National Vital Statistics System

Coronary heart disease death rates (age adjusted to the year 1940 standard population)*

	1990	1991	1992	1993	1994	1995	1996	1997	1998
White non-Hispanic	114.0	112.6	108.8	109.0	106.6	104.2	101.3	98.4	95.1
Black non-Hispanic	149.0	155.3	151.0	153.9	148.3	147.7	142.2	139.0	136.3
Hispanic	82.3	80.7	78.2	77.1	75.0	73.7	72.1	70.1	68.3
Am. Indian/ Alaska Native	76.7	79.0	81.3	81.2	77.7	75.9	74.3	75.4	70.1
Asian/Pacific Islander	62.5	62.6	62.7	59.4	60.2	57.8	56.4	54.6	53.6

*Age adjustment to the year 2000 standard population will begin in 1999.
SOURCE: CDC/NCHS, National Vital Statistics System

commentary and analysis



The Insignificance of Significance Testing

Abstract

Null hypothesis significance testing (NHST) is commonplace in atmospheric research, despite the many criticisms that have been leveled against its use in other fields of research. NHST is used, in papers in almost every issue of the Society's journals, to test correlations, means, and trends. Some of the major criticisms of NHST are summarized, and possible alternatives are discussed.

1. Introduction

Cohen (1994) noted that there had been trenchant criticism of null hypothesis significance testing (NHST) for four decades. These criticisms have been aired amongst statisticians, and in psychological, sociological, and medical research, and elsewhere. There have been discussions in some fields about whether NHST should be banned completely. Despite these discussions and criticisms, the use of NHST in atmospheric science remains common. Reviewers and editors sometimes insist on NHST to "test" correlations or trends. Presumably, many authors include significance tests of their results in the belief that their absence would likely prejudice reviewers or editors against publication.

I will cite a few recent atmospheric science papers of which I am a coauthor to illustrate some of the ways NHST is used. In each case, better statistical testing could probably have been adopted, but the pervasiveness of NHST biases authors toward this approach. Many other examples of NHST could have been presented here—these have been selected to demonstrate the pervasiveness of NHST in climate research. They are drawn from three different journals (not just from this Society). These examples will appear again later, in the discussion of criticisms of NHST.

The first example (Plummer et al. 1999) documented twentieth-century trends in a variety of climate extremes over Australia and New Zealand, and subjected these to NHST, highlighting the trends that were statistically significant. The second example (Manton et al. 2001) examined trends in extreme daily temperature and rainfall over Southeast Asia and the South Pacific in the period 1961–98. Most trends were illustrated just with maps with positive or negative symbols at stations to indicate the sign of the trend, with statistically significant trends denoted by bold symbols. The final example (Frederiksen et al. 2001) examined the skill of dynamical seasonal predictions during the 1997/98 El Niño. In maps of the skill of the forecasts, areas for which the skill did not reach statistically significant levels were left blank, even if these areas had positive skill. The use of NHST in each of these papers, and in many others, could be criticized. What is the basis for such criticisms?

2. Criticisms of NHST

To set the scene, consider a typical NHST for a specific study [a more complete description of hypothesis testing will be found in most statistics textbooks, e.g., Wilks (1995)]. The research could involve calculating a correlation between, say, the Southern Oscillation index (SOI) and winter snowfall at a specific location. The researcher might establish a null hypothesis, H_0, that there is no relationship (i.e., zero correlation) between the SOI and snowfall, if the entire population of data could be examined. The researcher would then calculate the correlation on a sample of data, for example, data from the period 1950–99. Standard tables would be used to calculate p, the probability that this correlation or a more extreme correlation would arise if a sample of the same size was drawn from a population with zero correlation. The correla-

tion would be deemed "statistically significant" if p was less than 0.05 (or possibly 0.01 or even 0.001). If p was larger than the threshold, the correlation would be labeled as "not significant." So what is wrong with such a procedure?

First, the test is arbitrary. For historical reasons, the test is usually performed as described above, with H_0 being "rejected" if $p < 0.05$. As Rosnell and Rosenthal (1989) noted however, "...surely, God loves the .06 nearly as much as the .05." In other words, why should a sample correlation strong enough to return $p < 0.06$, but not $p < 0.05$, be denoted as not statistically significant? The same argument applies no matter what value of p is used as the cutoff for significance. This problem arises just because of the dichotomous nature of NHST. The "blanking out" of areas on maps where some feature does not reach statistical significance is quite often seen in atmospheric science (e.g., Frederiksen et al. 2001). In other papers results that do not reach statistical significance are not displayed or listed. This method of display means that information is lost. For example, the skill in a specific area may be useful and real even if it does not reach the arbitrary 5% significance level. This problem could be avoided by reporting the actual p values, rather than using the NHST to separate statistically significant results from nonsignificant results.

It is possible that a specific effect does not reach the 5% significance level simply because of the small sample size. NHST is affected as much by the size of the sample as by the strength of the effect (e.g., the correlation) being tested. So, a correlation of 0.60 would be deemed "not significant ($p > 0.05$)" if the sample size was 10, but a correlation of 0.10 would be significant in a sample of 400. In general, a correlation of 0.60 would be considered more physically significant or useful than a correlation of 0.10. Yet the dependence of NHST on sample size means that we may overlook the strong correlation, but accept as "real" the smaller, potentially less useful correlation. An example of the sample-size problems that arise by relying on NHST comes from the early tests of the use of citrus fruit to treat and prevent scurvy (Maltz 1994). In 1747 the physician James Lind carried out an experiment by providing dietary additions to scurvy patients on the ship Salisbury. He used six dietary additions, one of which was citrus fruit. Lind assigned two sailors ill from scurvy to each treatment. Those who received the citrus fruit were cured in a few days and were able to help nurse the other patients. Maltz (1994) points out that this result would not have been significant at the 5% level, and thus would probably not be accepted by a modern journal that insists on NHST. So such results would probably be overlooked because of overreliance on significance testing.

The probability of rejecting the null hypothesis, with typically sized atmospheric data sets and effects, is actually rather smaller than many realize. Cohen (1990) provides an example that is very relevant to typical climate studies. He points out that the probability of a significance test of a correlation leading to the rejection of the null hypothesis is only 57% if the population, that is, *real* correlation, is 0.30, with a two-sided 0.05 alpha criterion and a sample size of 50. That is, the use of dichotomous NHST in such cases would lead to a real (and reasonably strong) correlation being discounted as not significant in nearly half the samples examined (if multiple samples were available). Despite the reasonable sample size (in climate terms) and the reasonably strong effect, the chance of wrongly not rejecting the null hypothesis is "a coin flip" (Cohen 1990).

Even if the null hypothesis is rejected, this is rarely very informative. The null hypothesis typically asserts that there is zero correlation between the variables, or zero difference in the mean between two treatments A and B. As noted by Tukey (1991), however, "It is foolish to ask 'Are the effects of A and B different?' They are always different—for some decimal place." Cohen (1994) has labeled the null hypothesis the "nil hypothesis" to illustrate the "ridiculous" nature of typical NHST. In general, we are really not interested in finding a statistically significant effect or correlation. As noted above, if we increase the sample size we will eventually find such an effect. We are more interested in physically and/or socially significant effects. Fixation on statistical significance can misdirect us from physically important processes or effects.

If the null hypothesis is not rejected, then the test is even less informative. It is often forgotten that if NHST does not lead to the rejection of the null hypothesis, this does not mean that it can be concluded that the null is true. All that can be concluded, in such a case, is that it cannot be concluded that the null hypothesis is false. "In other words, you could hardly conclude anything" (Cohen 1990). However, it is easy to fall into the trap of "accepting the null hypothesis" in such a situation.

There are also problems with the "samples" subjected to NHST in atmospheric research. At times NHST is used on a correlation or trend calculated from the entire population. One example occurred in the

Second Assessment of the Intergovernmental Panel on Climate Change (Nicholls et al. 1996), where the trends in global temperatures from surface observations, radiosondes, and the Microwave Sounding Unit satellite-based instrument were compared over the period 1979–95. These trends were different and it was important for the study to examine the causes of these differences. A reviewer pointed out, however, that NHST applied to these three series would not have led to rejection of the null hypothesis that there was zero trend. He then asserted that the trends therefore were indistinguishable from zero and each other, so the difference in trends should not have even been discussed. As described earlier, significance tests are applied to a statistic estimated from a sample taken from a population. But since all the 1979–95 data (i.e., the total population, rather than a sample) had been used to calculate the trends, then a significance test does not provide any extra information about the reality of the trends over this period. The only uncertainty would arise from measurement errors, not from sampling problems. An effect calculated using all the data for the period should not be subjected to a "significance test," since such a test is not, in fact, a test of statistical significance. The Plummer et al. (1999) and Manton et al. (2001) studies mentioned earlier also applied NHST to trends. The more important aspect of the magnitude of the trends can be lost in the question of whether they are statistically significant.

Samples of atmospheric data can diverge from the random samples assumed in NHST in other ways. In climate studies typically all the available data will be used for calculating correlations between, for instance, the SOI and snowfall. These data will typically exhibit serial correlation, and often also skewness, bimodality, and other deviations from well-behaved distributions. These deviations and problems can be overcome, and sometimes are overcome, through appropriate transformations and taking serial correlation into account. More often than not, however, it is simply assumed that these problems are not so severe as to invalidate classic NHST.

Perhaps a more fundamental problem with the samples in the atmospheric sciences, especially in climate studies, is that classic NHST does not apply to exploratory studies (Flueck and Brown 1993). In classic NHST, the researcher specifies the null and alternative hypotheses before examining the data. In many climate studies, the alternative hypothesis (e.g., that the SOI and snowfall are correlated) arises from an initial examination of the data. These same data cannot, then, be used as the sample for classic, a priori significance testing. Madden and Julian (1971) in their original paper on the 40–50-day oscillation note this problem with exploratory studies. Flueck and Brown point out that the "flexibility and searching nature of this type of study has dire effects on classical statistical inference statements." Most studies searching for climate trends are of the exploratory kind (e.g., Manton et al. 2001, Plummer et al. 1999). Trends are found in the data, which are then used as the "random" sample for NHST. This exploratory approach invalidates the use of classic NHST.

A common criticism of NHST is that it is often misinterpreted. Thus many researchers believe that significance tests answer the question "Given these data and the correlation calculated with them, what is the probability that H_0 is true (i.e., that there is zero correlation between the variables)?" In fact, the *p* value in NHST tells us "Given that H_0 is true, what is the probability of finding a correlation this strong (or stronger)?" These questions are not the same (Cohen 1994). However, it is easy to slip into the assumption that the questions are identical, thereby misinterpreting the NHST.

Another common misinterpretation is to equate "1-*p*" with the probability that the null hypothesis would be rejected if a second sample was available (i.e., the replicability of rejection of the null hypothesis). This fallacy is perhaps less common in climate work, mainly because of the difficulty of conceiving of a second sample becoming available, except after many years have passed. In fact, the probability of a second sample replicating the rejection of the null hypothesis, with the sample sizes and effect sizes typical in most research, is much lower than 1-*p*. In typical cases in the behavioral sciences (with similar effect and sample sizes to climate research) a *p* of 0.01 would typically mean that in five replications the chances of as many as three of them being significant would only be about 50% (Cohen 1994).

Rozeboom (1960) points out that NHST is essentially unscientific. The use of NHST implies that scientists should elect to adopt one belief or another, as a result of the data analysis and testing. Carver (1978) labeled NHST as a "corrupt form of the scientific method" because of this feature. Scientific experiments should help us make an appropriate adjustment in the degree to which we believe the hypothesis being tested, rather than a simple dichotomous decision about statistical significance. Reliance on NHST can lead us to dismiss data that actually support the re-

search hypothesis, simply because it does not reach statistical significance. This can mean that such data may not be combined with other, independent tests of the research hypothesis. An example of how this may affect atmospheric research relates to anthropogenic climate change detection. Most detection studies apply NHST to a sample of data, and determine whether to reject the null hypothesis of zero trend in the atmospheric variable under consideration. The data may, in one case, be the horizontal distribution of surface temperature trends; the next case may use the vertical distribution of temperature changes. Since these are somewhat independent pieces of evidence they should both help us adjust our beliefs in the probability that human influences are affecting climate. But treating these separately and individually to NHST means that two separate and unrelated "decisions" are made, and that the two data analyses do not provide a cumulative adjustment to our belief in climate change.

Sterling (1959) pointed out that fixation on NHST may lead to a bias in published scientific results. Thus, if a research project yields nonsignificant results, it will probably not be published. This research will, therefore, remain unknown to other researchers who may repeat the investigation on a different sample. Eventually one of these repeated investigations will yield a statistically significant result, and will be published. So, in a field where NHST is dominant, the published literature will consist of false conclusions arising from errors of the "first kind," that is, wrongly rejecting the null hypothesis.

Cohen (1990) and von Storch and Zwiers (1999) present other objections to the use of NHST. Loftus (1996) concludes his discussion of NHST with the statement that "the common belief that the precise quantity 0.05 refers to anything meaningful or interesting is illusory." Summarizing the arguments, Falk (1986) noted that "significance tests do not provide the information that scientists need, neither do they solve the crucial questions that they are characteristically believed to answer. The one answer that they do give, is not a question that we have asked. The conclusion that this practice should be dropped altogether seems inevitable." Although many of the problems with NHST arise because of misconceptions about what it means, these misconceptions are widespread, perhaps close to universal, and difficult to change (Falk and Greenbaum 1995). It seems unlikely that we will be able to overcome these misconceptions. So what can we do instead of NHST?

3. Alternatives to NHST

a Confidence intervals

One way to avoid some of the problems associated with NHST is to focus on the strength of the effect, rather than its statistical significance. This way we could focus further testing (a new sample, for instance, or testing in a physical model) on the strong effects rather than on weak but "significant" effects. This could be done, as well as retaining an indication of the confidence we should have in the results from the sample, by reporting confidence intervals around the effect size calculated from the sample. Gardner and Altman (1989) describe methods for calculating confidence intervals for correlations, regressions, differences of means, and a variety of other statistical measures. Wilks (1995) illustrates the computation and use of confidence intervals in atmospheric science research, and notes that, in a sense, confidence interval estimation is the inverse operation to NHST.

The reporting of confidence intervals would allow readers to address the question "Given these data and the correlation calculated with them, what is the probability that H_0 is true?" rather than "Given that H_0 is true, what is the probability of finding a correlation this strong (or stronger)?" If the interval included zero correlation then one may conclude that the evidence from the sample may not be strong enough, on its own, to determine the sign of the effect.

An important advantage of presenting a confidence interval is that it allows questions more relevant than the null hypothesis to be addressed. Reporting confidence intervals allows the testing of more useful hypotheses such as "Is there more than a weak correlation between the variables?" It includes the point estimate of the magnitude of the effect (instead of just reporting results as significant, as in, e.g., Manton et al. 2001). Other advantages of confidence intervals, as noted by Krantz (1999), are that a wide interval would reveal ignorance and thus dampen "optimism about replicability," and that if a second sample produced a confidence interval overlapping that of the original sample, this would not be considered a failure to replicate. This would not usually be the case with NHST where a nonsignificant effect on a second sample is often considered as nonreplication. As well, confidence intervals are formally valid, do not depend on a prior hypotheses, and do not result in trivial knowledge (Brandstätter 1999).

One problem with confidence intervals is that they, like NHST, are arbitrary, in the sense that the "width"

of the interval (e.g., 95%) must be specified. In some cases this arbitrariness might be overcome, to some degree, by having more than one interval (e.g., 50% and 95%), just as the same problem with NHST can be overcome by quoting several significance levels. But confidence intervals, despite this arbitrariness, do provide specific information concealed by NHST. Thus confidence intervals clearly reveal the precision of parameter estimates, with small intervals indicating more exact estimates than larger ones; they provide information on the magnitude of the effect of interest; and they are easier to understand than significance tests (Brandstätter 1999).

b. Permutation tests

Confidence intervals do not overcome the problem that many atmospheric empirical datasets are not random, well-behaved samples, and in some case are not even samples. From this point of view, confidence intervals suffer similar problems to NHST, in that intervals or significance levels are not formally valid. In such circumstances randomization tests, including bootstrap and Monte Carlo methods are a more effective way of addressing questions such as "What is the probability that H_0 is true?" Ludbrook and Dudley (1998) discuss the advantages of such tests, and the issue of the nonrandomness of samples in the atmospheric sciences is also discussed by Fluek and Brown (1993).

c. Cross validation and a posteriori testing

Confidence intervals also do not overcome the problems raised by the exploratory nature of much atmospheric research that invalidates the application of a priori tests such as NHST. Cross validation (e.g., Drosdowsky and Chambers 2001) can partly overcome this problem, producing a more realistic estimation of the reliability of an estimate of an effect in an exploratory study. Madden and Julian (1971) point out that in some cases a posteriori tests can also be devised to overcome this problem.

4. Are there situations where NHST could be used?

Hunter (1997) points out that NHST was originally designed for "debunking" studies of the following type. Suppose a researcher has strong reason to believe that a certain theory is false (e.g., that volcanic activity "triggers" El Niño events). The researcher will use a sample of data to examine the relationship between the variables. If the population effect size is actually zero, sampling error will still cause the observed result to differ from zero. The significance test was developed to see if the deviation from zero effect is too large to be credible. However, most uses of significance tests are not debunking studies, but in fact start from the hypothesis that there is an effect (sometimes based on earlier research by others). For such studies (labeled "confirmatory studies" by Hunter 1997), the significance tests are inappropriate because the earlier work almost guarantees that the null hypothesis is not true. That is, the earlier work or theoretical considerations suggest the existence of an effect of some magnitude—the purpose of the "confirmatory" test, then, is mainly to estimate the strength of this effect. This is more readily done with confidence intervals. NHST helps little in such studies.

One possible use of NHST in atmospheric science is where correlations (or differences in means) are displayed as a map (e.g., the correlation between the SOI and global sea surface temperatures). Here the use of confidence intervals would result in a very complex map. Perhaps in this instance shading could identify those regions where the correlations were larger than might be expected if H_0 were true. But even in this instance, such mapping should only be a preliminary to the calculation of confidence intervals around what appear to be the most interesting correlations, and the map should still display correlations even where H_0 was not rejected with NHST.

In general, however, NHST tells us little of what we need to know and is inherently misleading. We should be less enthusiastic about insisting on its use.

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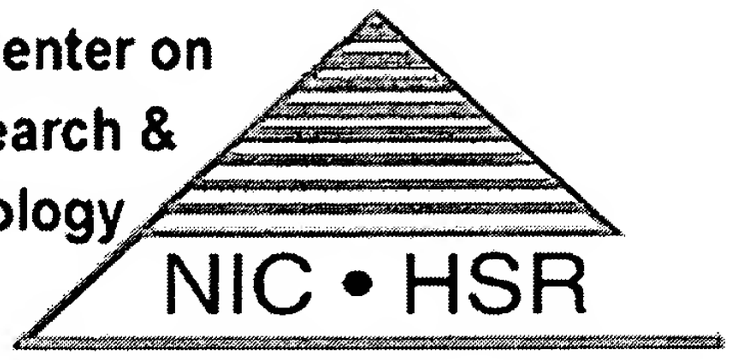

GLOSSARY

Absolute risk reduction: a measure of treatment effect that compares the probability (or mean) of a type of outcome in the control group with that of a treatment group, [i.e.: P_c - P_t (or μ_c - μ_t)]. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the absolute risk reduction would be (0.25 - 0.10) = 0.15. (See also **number needed to treat, odds ratio,** and **relative risk reduction.**)

Accuracy: the degree to which a measurement (e.g., the mean estimate of a treatment effect) is true or correct. An estimate can be accurate, yet not be precise, if it is based upon an unbiased method that provides observations having great variation (i.e., not close in magnitude to each other). (Contrast with **precision.**)

Alpha (a): the probability of a Type I (false-positive) error. In hypothesis testing, the a-level is the threshold for defining statistical significance. For instance, setting a at a level of 0.05 implies that investigators accept that there is a 5% chance of concluding incorrectly that an intervention is effective when it has no true effect. The a-level is commonly set at 0.01 or 0.05 or 0.10.

Benchmarking: a quality assurance process in which an organization sets goals and measures its performance in comparison to those of the products, services, and practices of other organizations that are recognized as leaders.

Beta (b): the probability of a Type II (false-negative) error. In hypothesis testing, b is the probability of concluding incorrectly that an intervention is not effective when it has true effect. (1-b) is the **power** to detect an effect of an intervention if one truly exists.

Bias: in general, any factor that distorts the true nature of an event or observation. In clinical investigations, a bias is any systematic factor other than the intervention of interest that affects the magnitude of (i.e., tends to increase or decrease) an observed difference in the outcomes of a treatment group and a control group. Bias diminishes the accuracy (though not necessarily the precision) of an observation. Randomization is a technique used to decrease this form of bias. Bias also refers to a prejudiced or partial viewpoint that would affect someone's interpretation of a problem. Double blinding is a technique used to decrease this type of bias.

Bibliographic database: an indexed computer or printed source of citations of journal articles and other reports in the literature. Bibliographic citations typically include author, title, source, abstract, and/or related information (including full text in some cases). Examples are *MEDLINE* and *EMBASE.*

Blinding: the concealment of group assignment (to either the treatment or control group) from the knowledge of patients and/or investigators in a clinical trial. Blinding eliminates the possibility that knowledge of assignment may affect patient response to treatment or investigator behaviors that may affect outcomes. Blinding is not always practical (e.g. when comparing surgery to drug treatment),

but it should be used whenever it is possible and compatible with optimal patient care. A **single-blind** trial is one in which knowledge of group assignment is withheld only from patients; a **double-blind** trial is one in which the knowledge is withheld from patients and investigators.

Case-control study: a retrospective observational study in which investigators identify a group of patients with a specified outcome (cases) and a group of patients without the specified outcome (controls). Investigators then compare the histories of the cases and the controls to determine the extent to which each was exposed to the intervention of interest.

Case study: an uncontrolled (prospective or retrospective) observational study involving an intervention and outcome in a single patient. (Also known as a single case report or anecdote.)

Citation: the record of an article, book, or other report in a bibliographic database that includes summary descriptive information, e.g., authors, title, abstract, source, and indexing terms.

Clinical pathway: a multidisciplinary set of daily prescriptions and outcome targets for managing the overall care of a specific type of patient, e.g., from pre-admission to post-discharge for patients receiving inpatient care. Clinical pathways often are intended to maintain or improve quality of care and decrease costs for patients in particular diagnosis-related groups.

Clinical practice guidelines: a systematically developed statement to assist practitioner and patient decisions about appropriate health care for one or more specific clinical circumstances. The development of clinical practice guidelines can be considered to be a particular type of HCTA; or, it can be considered to be one of the types of policymaking that is informed or supported by HCTA.

Clinical significance: a conclusion that an intervention has an effect that is of practical meaning to patients and health care providers. Even though an intervention is found to have a statistically significant effect, this effect might not be clinically significant. In a trial with a large number of patients, a small difference between treatment and control groups may be statistically significant but clinically unimportant. In a trial with few patients, an important clinical difference may be observed that does not achieve statistical significance. (A larger trial may be needed to confirm that this is a statistically significant difference.)

Cohort study: an observational study in which outcomes in a group of patients that received an intervention are compared with outcomes in a similar group i.e., the cohort, either contemporary or historical, of patients that did not receive the intervention. In an adjusted- (or matched-) cohort study, investigators identify (or make statistical adjustments to provide) a cohort group that has characteristics (e.g., age, gender, disease severity) that are as similar as possible to the group that experienced the intervention.

Compliance: a measure of the extent to which patients undergo an assigned treatment or regimen, e.g., taking drugs, undergoing a medical or surgical procedure, doing an exercise regimen, or abstaining from smoking.

Concurrent nonrandomized control: a control group that is observed by investigators at the same time as the treatment group, but that was not established using random assignment of patients to control and treatment groups. Differences in the composition of the treatment and control groups may result.

Confidence interval: depicts the range of uncertainty about an estimate of a treatment effect. It is calculated from the observed differences in outcomes of the treatment and control groups and the sample size of a study. The confidence interval is the range of values above and below the point estimate that is likely to include the true value of the treatment effect. The use of confidence intervals assumes that a study provides one sample of observations out of many possible samples

that would be derived if the study were repeated many times. Investigators typically use confidence intervals of 90%, 95%, or 99%. For instance, there is a 95% probability that a 95% confidence interval calculated from a particular study includes the true value of a treatment effect. If the interval includes a null treatment effect (usually 0.0 but 1.0 if the treatment effect measure used is an odds ratio or relative risk), the null hypothesis of no true treatment effect cannot be rejected.

Confidence profile method: a type of meta-analysis based on Bayesian statistics for combining results of multiple studies of various design (e.g., RCTs, observational studies, and others) that adjusts the individual studies for their respective methodological biases before combining their results into a probability distribution for the parameter(s) of interst.

Consensus development: various forms of group judgment in which a group (or panel) of experts interacts in assessing an intervention and formulating findings by vote or other process of reaching general agreement. These process may be informal or formal, involving such techniques as the nominal group and Delphi techniques.

Contraindication: a clinical symptom or circumstance indicating that the use of an otherwise advisable intervention would be inappropriate.

Control group: a group of patients that serves as the basis of comparison when assessing the effects of the intervention of interest that is given to the patients in the treatment group. Depending upon the circumstances of the trial, a control group may receive no treatment, a "usual" or "standard" treatment, or a placebo. To make the comparison valid, the composition of the control group should resemble that of the treatment group as closely as possible. (See also **historical control** and **concurrent nonrandomized control**.)

Controlled vocabulary: a system of terms, involving, e.g., definitions, hierarchical structure, and cross-references, that is used to index and retrieve a body of literature in a bibliographic, factual, or other database. An example is the *MeSH* controlled vocabulary used in *MEDLINE* and other *MEDLARS* databases of the NLM.

Cost-benefit analysis: a comparison of alternative interventions in which costs and outcomes are quantified in common monetary units.

Cost-effectiveness analysis: a comparison of alternative interventions in which costs are measured in monetary units and outcomes are measured in non-monetary units, e.g., reduced mortality or morbidity.

Cost-minimization analysis: a determination of the least costly among alternative interventions that are assumed to produce equivalent outcomes.

Cost-utility analysis: a form of cost-effectiveness analysis of alternative interventions in which costs are measured in monetary units and outcomes are measured in terms of their utility, usually to the patient, e.g., using QALYs.

Cost of illness analysis: a determination of the economic impact of an disease or health condition, including treatment costs; this form of study does not address benefits/outcomes.

Crossover bias: occurs when some patients who are assigned to the treatment group in a clinical study do not receive the intervention or receive another intervention, or when some patients in the control group receive the intervention (e.g., outside the trial). If these crossover patients are analyzed with their original groups, this type of bias can "dilute" (diminish) the observed treatment effect.

Crossover design: a clinical trial design in which patients receive, in sequence, the treatment (or the

control), and then, after a specified time, switch to the control (or treatment). In this design, patients serve as their own controls, and randomization is used to determine the order in which a patient receives the treatment and control.

Cross-sectional study: a (prospective or retrospective) observational study in which a group is chosen (sometimes as a random sample) from a certain larger population, and the exposures of people in the group to an intervention and outcomes of interest are determined.

Database (or register): any of a wide variety of repositories (often computerized) for observations and related information about a group of patients (e.g., adult males living in Göteborg) or a disease (e.g., hypertension) or an intervention (e.g., antihypertensive drug therapy) or other events or characteristics. Depending upon criteria for inclusion in the database, the observations may have controls. Although these can be useful, a variety of confounding factors (e.g., no randomization and possible selection bias in the process by which patients or events are recorded) make them relatively weak methods for determining causal relationships between an intervention and an outcome.

Decision analysis: an approach to decision making under conditions of uncertainty that involves modeling of the sequences or pathways of multiple possible strategies (e.g., of diagnosis and treatment for a particular clinical problem) to determine which is optimal. It is based upon available estimates (drawn from the literature or from experts) of the probabilities that certain events and outcomes will occur and the values of the outcomes that would result from each strategy. A decision tree is a graphical representation of the alternate pathways.

Delphi technique: an iterative group judgment technique in which a central source forwards surveys or questionnaires to isolated, anonymous (to each other) participants whose responses are collated/summarized and recirculated to the participants in multiple rounds for further modification/critique, producing a final group response (sometimes statistical).

Direct costs: the fixed and variable costs of all resources (goods, services, etc.) consumed in the provision of an intervention as well as any consequences of the intervention such as adverse effects or goods or services induced by the intervention. Includes direct medical costs and direct nonmedical costs such as transportation or child care.

Disability-adjusted life years (DALYs): a unit of health care status that adjusts age-specific life expectancy by the loss of health and years of life due to disability from disease or injury. DALYs are often used to measure the global burden of disease.

Discounting: the process used in cost analyses to reduce mathematically future costs and/or benefits/outcomes to their present value, e.g., at an annual rate of five or ten percent. These adjustments reflect that given levels of costs and benefits occurring in the future usually have less value in the present than the same levels of costs and benefits realized in the present.

Disease management: a systematic process of managing care of patients with specific diseases or conditions (particularly chronic conditions) across the spectrum of outpatient, inpatient, and ancillary services. The purposes of disease management may include: reduce acute episodes, reduce hospitalizations, reduce variations in care, improve health outcomes, and reduce costs. Disease management may involve continuous quality improvement or other management paradigms. It may involve a cyclical process of following practice protocols, measuring the resulting outcomes, feeding those results back to clinicians, and revising protocols as appropriate.

Dissemination: any process by which information is transmitted (made available or accessible) to intended audiences or target groups.

Effect size: same as **treatment effect**. Also, a dimensionless measure of treatment effect that is

typically used for continuous variables and is usually defined as the difference in mean outcomes of the treatment and control group divided by the standard deviation of the outcomes of the control group. One type of meta-analysis involves averaging the effect sizes from multiple studies.

Effectiveness: the benefit (e.g., to health outcomes) of using a technology for a particular problem under general or routine conditions, for example, by a physician in a community hospital or by a patient at home.

Effectiveness research: see **outcomes research.**

Efficacy: the benefit of using a technology for a particular problem under ideal conditions, for example, in a laboratory setting, within the protocol of a carefully managed randomized controlled trial, or at a "center of excellence."

Endpoint: a measure or indicator chosen for determining an effect of an intervention.

Evidence-based medicine: the use of current best evidence from scientific and medical research to make decisions about the care of individual patients. It involves formulating questions relevant to the care of particular patients, searching the scientific and medical literature, identifying and evaluating relevant research results, and applying the findings to patients.

Evidence table: a summary display of selected characteristics (e.g., of methodological design, patients, outcomes) of studies of a particular intervention or health problem.

External validity: the extent to which the findings obtained from an investigation conducted under particular circumstances can be generalized to other circumstances. To the extent that the circumstances of a particular investigation (e.g., patient characteristics or the manner of delivering a treatment) differ from the circumstances of interest, the external validity of the findings of that investigation may be questioned.

Factual database: an indexed computer or printed source that provides information in the form of guidelines for diagnosis and treatment, patient indications, or other authoritative information. Examples are *PDQ,* a computer database on cancer management, and *DRUGLINE,* a computer database on drug indications, contraindications, and interactions.

False negative error: occurs when the statistical analysis of a trial detects no difference in outcomes between a treatment group and a control group when in fact a true difference exists. This is also known as a **Type II error**. The probability of making a Type II error is known as b.

False positive error: occurs when the statistical analysis of a trial detects a difference in outcomes between a treatment group and a control group when in fact there is no difference. This is also known as a **Type I error**. The probability of a Type I error is known as a.

Follow-up: the ability of investigators to observe and collect data on all patients who were enrolled in a trial for its full duration. To the extent that data on patient events relevant to the trial are lost, e.g., among patients who move away or otherwise withdraw from the trial, the results may be affected, especially if there are systematic reasons why certain types of patients withdraw. Investigators should report on the number and type of patients who could not be evaluated, so that the possibility of bias may be considered.

Gray literature: research reports that are not found in traditional peer-reviewed publications, for example: government agency monographs, symposium proceedings, and unpublished company reports.

Health care technology assessment (HCTA): the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. HCTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

Health-related quality of life (HRQL) measures: patient outcome measures that extend beyond traditional measures of mortality and morbidity, to include such dimensions as physiology, function, social activity, cognition, emotion, sleep and rest, energy and vitality, health perception, and general life satisfaction. (Some of these are also known as health status, functional status, or quality of life measures.)

Health services research: a field of inquiry that examines the impact of the organization, financing and management of health care services on the delivery, quality, cost, access to and outcomes of such services.

Healthy-years equivalents (HYEs): the number of years of perfect health that are considered equivalent to (i.e., have the same utility as) the remaining years of life in their respective health states.

Historical control: a control group that is chosen from a group of patients who were observed at some previous time. The use of historical controls raises concerns about valid comparisons because they are likely to differ from the current treatment group in their composition, diagnosis, disease severity, determination of outcomes, and/or other important ways that would confound the treatment effect. It may be feasible to use historical controls in special instances where the outcomes of a standard treatment (or no treatment) are well known and vary little for a given patient population.

Hypothesis testing: a means of interpreting the results of a clinical trial that involves determining the probability that an observed treatment effect could have occurred due to chance alone if a specified hypothesis were true. The specified hypothesis is normally a **null hypothesis,** made prior to the trial, that the intervention of interest has no true effect. Hypothesis testing is used to determine if the null hypothesis can or cannot be rejected.

Incidence: the rate of occurrence of new cases of a disease or condition in a population at risk during a given period of time, usually one year.

Indication: a clinical symptom or circumstance indicating that the use of a particular intervention would be appropriate.

Indirect costs: the cost of time lost from work and decreased productivity due to disease, disability, or death. (In cost accounting, it refers to the the overhead or fixed costs of producing goods or services.)

Intangible costs: the cost of pain and suffering resulting from a disease, condition, or intervention.

Internal validity: the extent to which the findings of a study accurately represent the causal relationship between an intervention and an outcome in the particular circumstances of that study. The internal validity of a trial can be suspect when certain types of biases in the design or conduct of a trial could have affected outcomes, thereby obscuring the true direction, magnitude, or certainty of the treatment effect.

Investigational Device Exemption (IDE): a regulatory category and process in which the U.S. Food and Drug Administration (FDA) allows specified use of an unapproved health device in controlled settings for purposes of collecting data on safety and efficacy/effectiveness; this

information may be used subsequently in a premarketing approval application.

Investigational New Drug Application (IND): an application submitted by a sponsor to the U.S. FDA prior to human testing of an unapproved drug or of a previously approved drug for an unapproved use.

Large, simple trials: prospective, randomized controlled trials that use large numbers of patients, broad patient inclusion criteria, multiple study sites, minimal data requirements, and electronic registries; their purposes include detecting small and moderate treatment effects, gaining effectiveness data, and improving external validity.

Literature review: a summary and interpretation of research findings reported in the literature. May include unstructured qualitative reviews by single authors as well as various systematic and quantitative procedures such as meta-analysis. (Also known as overview.)

Marginal benefit: the additional benefit (e.g., in units of health outcome) produced by an additional resource use (e.g., another health care intervention).

Marginal cost: the additional cost required to produce an additional unit of benefit (e.g., unit of health outcome).

Markov model: A type of quantitative modeling that involves a specified set of mutually exclusive and exhaustive states (e.g., of a given health status), and for which there are transition probabilities of moving from one state to another (including of remaining in the same state). Typically, states have a uniform time period, and transition probabilities remain constant over time.

MEDLARS: the *Med*ical *L*iterature *A*nalysis and *R*etrieval *S*ystem of about 40 computer databases managed by the U.S. NLM.

MEDLINE: a bibliographic database that is the most used of about 40 *MEDLARS* databases managed by the U.S. NLM. It is the computer version of the printed *Index Medicus.* Citations for 7.5 million articles published since 1966 from about 3,700 health and biomedical journals are compiled in *MEDLINE,* which is updated at a rate of 6,600 articles every week. About 75% of citations are for English-language articles.

MeSH: *Me*dical *S*ubject *H*eadings, the controlled vocabulary of about 16,000 terms used for *MEDLINE* and certain other *MEDLARS* databases.

Meta-analysis: systematic methods that use statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. This combination may produce a stronger conclusion than can be provided by any individual study. (Also known as data synthesis or quantitative overview.)

Moving target problem: changes in health care that can render the findings of HCTAs out of date, sometimes before their results can be implemented. Included are changes in the focal technology, changes in the alternative or complementary technologies i.e., that are used for managing a given health problem, emergence of new competing technologies, and changes in the application of the technology (e.g., to different patient populations or to different health problems).

N of 1 trial: a clinical trial in which a single patient is the total population for the trial, including a single case study. An N of 1 trial in which random allocation is used to determine the order in which an experimental and a control intervention are given to a patient is an N of 1 RCT.

New Drug Application (NDA): an application submitted by a sponsor to the FDA for approval to

market a new drug (a new, nonbiological molecular entity) for human use in U.S. interstate commerce.

Nominal group technique: a face-to-face group judgment technique in which participants generate silently, in writing, responses to a given question/problem; responses are collected and posted, but not identified by author, for all to see; responses are openly clarified, often in a round-robin format; further iterations may follow; and a final set of responses is established by voting/ranking.

Null hypothesis: in hypothesis testing, the hypothesis that an intervention has no effect, i.e., that there is no true difference in outcomes between a treatment group and a control group. Typically, if statistical tests indicate that the *P* value is at or above the specified a-level (e.g., 0.01 or 0.05), then any observed treatment effect is not statistically significant, and the null hypothesis cannot be rejected. If the P value is less than the specified a-level, then the treatment effect is statistically significant, and the null hypothesis is rejected. If a confidence interval (e.g., of 95% or 99%) includes zero treatment effect, then the null hypothesis cannot be rejected.

Number needed to treat: a measure of treatment effect that provides the number of patients who need to be treated to prevent one outcome event. It is the inverse of absolute risk reduction (1 , absolute risk reduction); i.e., 1.0 , (P_c - P_t). For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the number needed to treat would be 1.0 , (0.25 - 0.10) = 6.7 patients. (See also **absolute risk reduction, relative risk reduction,** and **odds ratio.)**

Observational study: a study in which the investigators do not manipulate the use of an intervention (e.g., do not randomize patients to treatment and control groups), but only observe patients who are (and sometimes patients who are not) exposed to the intervention, and interpret the outcomes.

Odds ratio: a measure of treatment effect that compares the probability of a type of outcome in the treatment group with the outcome of a control group, i.e., [P_t , (1 - P_t)] , [P_c , (1 - P_c)]. For instance, if the results of a trial were that the probability of death in a control group was 25% and the probability of death in a treatment group was 10%, the odds ratio of survival would be [0.10 , (1.0 - 0.10)] , [(0.25 , (1.0 - 0.25)] = 0.33. (See also **absolute risk reduction, number needed to treat,** and **relative risk.**)

Outcomes research: evaluates the impact of health care on the health outcomes of patients and populations. It may also include evaluation of economic impacts linked to health outcomes, such as cost effectiveness and cost utility. Outcomes research emphasizes health problem- (or disease-) oriented evaluations of care delivered in general, real-world settings; multidisciplinary teams; and a wide range of outcomes, including mortality, morbidity, functional status, mental well-being, and other aspects of health-related quality of life. It may entail any in a range of primary data collection methods and synthesis methods that combine data from primary studies.

***P* value:** in hypothesis testing, the probability that an observed difference between the intervention and control groups is due to chance alone if the null hypothesis is true. If *P* is less than the a-level (typically 0.01 or 0.05) chosen prior to the study, then the null hypothesis is rejected.

Parallel (or independent groups) design: a trial that compares two groups of patients, one of which receives the treatment of interest and one of which is a control group (e.g., a randomized controlled trial). (Some parallel trials have more than one treatment group; others compare two treatment groups, each acting as a control for the other.)

Patient selection bias: a bias that occurs when patients assigned to the treatment group differ from patients assigned to the control group in ways that can affect outcomes, e.g., age or disease severity.

If the two groups are constituted differently, it is difficult to attribute observed differences in their outcomes to the intervention alone. Random assignment of patients to the treatment and control groups minimizes opportunities for this bias.

Peer review: the process by which manuscripts submitted to health, biomedical, and other scientifically oriented journals and other publications are evaluated by experts in appropriate fields (usually anonymous to the authors) to determine if the manuscripts are of adequate quality for publication.

Phase I, II, III, and IV studies: phases of clinical trials of new technologies (usually drugs) in the development and approval process required by the FDA (or other regulatory agencies). Phase I trials usually involve approximately 20-80 healthy volunteers to determine a drug's safety, safe dosage range, absorption, metabolic activity, excretion, and the duration of activity. Phase II trials are controlled trials in approximately 100-300 volunteer patients (with disease) to determine the drug's efficacy and adverse reactions (sometimes divided into Phase IIa pilot trials and Phase IIb well-controlled trials). Phase III trials are larger controlled trials in approximately 1,000-3,000 patients to verify efficacy and monitor adverse reactions during longer-term use (sometimes divided into Phase IIIa trials conducted before regulatory submission and Phase IIIb trials conducted after regulatory submission but before approval). Phase IV trials are postmarketing studies to monitor long-term effects and provide additional information on safety and efficacy, including for different regimens patient groups.

Placebo: an inactive substance or treatment given to satisfy a patient's expectation for treatment. In some controlled trials (particularly investigations of drug treatments) placebos that are made to be indistinguishable by patients (and providers when possible) from the true intervention are given to the control group to be used as a comparative basis for determining the effect of the investigational treatment.

Placebo effect: the effect on patient outcomes (improved or worsened) that may occur due to the expectation by a patient (or provider) that a particular intervention will have an effect. The placebo effect is independent of the true effect (pharmacological, surgical, etc.) of a particular intervention. To control for this, the control group in a trial may receive a placebo.

Power: the probability of detecting a treatment effect of a given magnitude when a treatment effect of at least that magnitude truly exists. For a true treatment effect of a given magnitude, power is the probability of avoiding Type II error, and is generally defined as (1 - b).

Precision: the degree to which a measurement (e.g., the mean estimate of a treatment effect) is derived from a set of observations having small variation (i.e., close in magnitude to each other). A precise estimate is not necessarily an accurate one. (Contrast with **accuracy.**)

Predictive value negative: an operating characteristic of a diagnostic test; predictive value negative is the proportion of persons with a negative test who truly do not have the disease, determined as: [true negatives _ (true negatives + false negatives)]. It varies with the prevalence of the disease in the population of interest. (Contrast with **predictive value negative.**)

Predictive value positive: an operating characteristic of a diagnostic test; predictive value positive is the proportion of persons with a positive test who truly have the disease, determined as: [true positives ¸ (true positives + false positives)]. It varies with the prevalence of the disease in the population of interest. (Contrast with **predictive value negative.**)

Premarketing Approval (PMA) Application: an application made by the sponsor of a health device to the FDA for approval to market the device in U.S. interstate commerce. The application includes information documenting the safety and efficacy/effectiveness of the device.

Prevalence: the number of people in a population with a specific disease or condition at a given time, usually expressed as a ratio of the number of affected people to the total population.

Primary study: an investigation that collects original (primary) data from patients, e.g., randomized controlled trials, observational studies, series of cases, etc. (Contrast with **synthetic/integrative study**).

Probability distribution: portrays the relative likelihood that a range of values is the true value of a treatment effect. This distribution is typically shown in the form of a bell-shaped curve. An estimate of the most likely true value of the treatment effect is the value at the highest point of the distribution. The area under the curve between any two points along the range gives the probability that the true value of the treatment effect lies between those two points. Thus, a probability distribution can be used to determine an interval that has a designated probability (e.g., 95%) of including the true value of the treatment effect.

Prospective study: a study in which the investigators plan and manage the intervention of interest in selected groups of patients. As such, investigators do not know what the outcomes will be when they undertake the study. (Contrast with **retrospective study**.)

Publication bias: unrepresentative publication of research reports that is not due to the quality of the research but to other characteristics, e.g., tendencies of investigators to submit, and publishers to accept, positive research reports (i.e., ones with results showing a beneficial treatment effect of a new intervention).

Quality-adjusted life year (QALY): a unit of health care outcomes that adjusts gains (or losses) in years of life subsequent to a health care intervention by the quality of life during those years. QALYs can provide a common unit for comparing cost-utility across different interventions and health problems. Analogous units include disability-adjusted life years (DALYs) and healthy-years equivalents (HYEs).

Quality assessment: a measurement and monitoring function of quality assurance for determining how well health care is delivered in comparison with applicable standards or acceptable bounds of care.

Quality assurance: activities intended to ensure that the best available knowledge concerning the use of health care to improve health outcomes is properly implemented. This involves the implementation of health care standards, including quality assessment and activities to correct, reduce variations in, or otherwise improve health care practices relative to these standards.

Quality of care: the degree to which health care is expected to increase the likelihood of desired health outcomes and is consistent with standards of health care. (See also **quality assessment** and **quality assurance**.)

Random variation (or random error): the tendency for the estimated magnitude of a parameter (e.g., based upon the average of a sample of observations of a treatment effect) to deviate randomly from the true magnitude of that parameter. Random variation is independent of the effects of systematic biases. In general, the larger the sample size is, the lower the random variation is of the estimate of a parameter. As random variation decreases, precision increases.

Randomization: a technique of assigning patients to treatment and control groups that is based only on chance distribution. It is used to diminish patient selection bias in clinical trials. Proper randomization of patients is an indifferent yet objective technique that tends to neutralize patient prognostic factors by spreading them evenly among treatment and control groups. Randomized assignment is often based on computer-generated tables of random numbers.

Randomized controlled trial (RCT): a true prospective experiment in which investigators randomly assign an eligible sample of patients to one or more treatment groups and a control group and follow patients' outcomes. (Also known as **randomized clinical trial**.)

Receiver operating characteristic (ROC) curve: a graphical depiction of the relationship between the true positive ratio (sensitivity) and false positive ratio (1 - specificity) as a function of the cutoff level of a disease (or condition) marker. ROC curves help to demonstrate how raising or lowering the cutoff point for defining a positive test result affects tradeoffs between correctly identifying people with a disease (true positives) and incorrectly labeling a person as positive who does not have the condition (false positives).

Register: see **database**.

Reliability: the extent to which an observation that is repeated in the same, stable population yields the same result (i.e., test-retest reliability). Also, the ability of a single observation to distinguish consistently among individuals in a population.

Relative risk reduction: a type of measure of treatment effect that compares the probability of a type of outcome in the treatment group with that of a control group, i.e.: $(P_c - P_t)$, P_c. For instance, if the results of a trial show that the probability of death in a control group was 25% and the probability of death in a control group was 10%, the relative risk reduction would be: (0.25 - 0.10) , 0.25 = 0.6. (See also **absolute risk reduction, number needed to treat,** and **odds ratio**.)

Retrospective study: a study in which investigators select groups of patients that have already been treated and analyze data from the events experienced by these patients. These studies are subject to bias because investigators can select patient groups with known outcomes. (Contrast with **prospective study**.)

Safety: a judgment of the acceptability of risk (a measure of the probability of an adverse outcome and its severity) associated with using a technology in a given situation, e.g., for a patient with a particular health problem, by a clinician with certain training, or in a specified treatment setting.

Sample size: the number of patients studied in a trial, including the treatment and control groups, where applicable. In general, a larger sample size decreases the probability of making a false-positive error (a) and increases the power of a trial, i.e., decreases the probability of making a false-negative error (b). Large sample sizes decrease the effect of random variation on the estimate of a treatment effect.

Sensitivity: an operating characteristic of a diagnostic test that measures the ability of a test to detect a disease (or condition) when it is truly present. Sensitivity is the proportion of all diseased patients for whom there is a positive test, determined as: [true positives , (true positives + false negatives)]. (Contrast with **specificity.**)

Sensitivity analysis: a means to determine the robustness of a mathematical model or analysis (such as a cost-effectiveness analysis or decision analysis) that tests a plausible range of estimates of key independent variables (e.g., costs, outcomes, probabilities of events) to determine if such variations make meaningful changes the results of the analysis. Sensitivity analysis also can be performed for other types of study; e.g., clinical trials analysis (to see if inclusion/exclusion of certain data changes results) and meta-analysis (to see if inclusion/exclusion of certain studies changes results).

Series: an uncontrolled study (prospective or retrospective) of a series (succession) of consecutive patients who receive a particular intervention and are followed to observe their outcomes. (Also known as **clinical series** or **series of consecutive cases.**)

Specificity: an operating characteristic of a diagnostic test that measures the ability of a test to exclude the presence of a disease (or condition) when it is truly not present. Specificity is the proportion of nondiseased patients for whom there is a negative test, expressed as: [true negatives , (true negatives + false positives)]. (Contrast with **sensitivity.**)

Statistical significance: a conclusion that an intervention has a true effect, based upon observed differences in outcomes between the treatment and control groups that are sufficiently large so that these differences are unlikely to have occurred due to chance, as determined by a statistical test. Statistical significance indicates the probability that the observed difference was due to chance if the null hypothesis is true; it does not provide information about the magnitude of a treatment effect. (Statistical significance is necessary but not sufficient for **clinical significance**.)

Statistical test: a mathematical formula (or function) that is used to determine if the difference in outcomes of a treatment and control group are great enough to conclude that the difference is statistically significant. Statistical tests generate a value that is associated with a particular *P* value. Among the variety of common statistical tests are: *F, t, Z,* and *chi-square.* The choice of a test depends upon the conditions of a study, e.g., what type of outcome variable used, whether or not the patients were randomly selected from a larger population, and whether it can be assumed that the outcome values of the population have a normal distribution or other type of distribution.

Surrogate endpoint: an outcome measure that is used in place of a primary endpoint (outcome). Examples are decrease in blood pressure as a predictor of decrease in strokes and heart attacks in hypertensive patients, and increase in T-cell (a type of white blood cell) counts as an indicator of improved survival of AIDS patients. Use of a surrogate endpoint assumes that it is a reliable predictor of the primary endpoint(s) of interest.

Synthetic (or integrative) study: a study that does not generate primary data but that involves the qualitative or quantitative consolidation of findings from multiple primary studies. Examples are literature review, meta-analysis, decision analysis, and consensus development. (Contrast with primary study.)

Technological imperative: the inclination to use a technology that has potential for some benefit, however marginal or unsubstantiated, based on an abiding fascination with technology, the expectation that new is better, and financial and other professional incentives.

Technology: the application of scientific or other organized knowledge--including any tool, technique, product, process, method, organization or system--to practical tasks. In health care, technology includes drugs; diagnostics, indicators and reagents; devices, equipment and supplies; medical and surgical procedures; support systems; and organizational and managerial systems used in prevention, screening, diagnosis, treatment and rehabilitation.

Treatment effect: the effect of a treatment (intervention) on outcomes, i.e., attributable only to the effect of the intervention. Investigators seek to estimate the true treatment effect using the difference between the observed outcomes of a treatment group and a control group. (See **effect size**.)

Type I error: same as **false-positive error**.

Type II error: same as **false-negative error.**

Utility: the relative desirability or preference (usually from the perspective of a patient) for a specific health outcome or level of health status.

Validity: The extent to which a measure accurately reflects the concept that it is intended to measure.

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VassarStats

For a 2x2 Contingency Table:
·Rates, Risk Ratio, Odds, Odds Ratio, Log Odds
·Phi Coefficient of Association
·Chi-Square Test of Association
·Fisher Exact Probability Test

For two groups of subjects, each sorted according to the absence or presence of some particular characteristic or condition, this page will calculate standard measures for Rates, Risk Ratio, Odds, Odds Ratio, and Log Odds. It will also

- calculate the Phi coefficient of association;
- perform a chi-square test of association, if the sample size is not too small; and
- perform the Fisher exact probability test, if the sample size is not too large.
- For intermediate values of n, the chi-square and Fisher tests will both be performed.

To proceed, enter the 'condition absent' and 'condition present' frequency values for the two groups into the designated cells. When all four cell values have been entered, click the 'Calculate' button. To perform a new analysis with a new set of data, click the 'Reset' button.

The logic and computational details of the Chi-Square and Fisher tests are described in Chapter 8 and Subchapter 8a, respectively, of Concepts and Applications.

Data Entry:

	Condition absent	Condition present	Totals		Expected Cell Frequencies per Null Hypothesis: absent	present
Group 1	598	115	713		615.31	97.69
Group 2	624	79	703	Reset	606.69	96.31
Totals	1222	194	1416	Calculate		

	Rate	Risk Ratio	Odds	Odds Ratio	Log Odds
Group 1	0.1613	1.4353	0.1923	1.519	0.418
Group 2	0.1124		0.1266		

Rate = proportion in group with condition present
Risk Ratio = Rate[1]/Rate[2]
Odds[1] = present[1]/absent[1]
Odds[2] = present[2]/absent[2]
Odds Ratio = Odds[1]/Odds[2]

Log Odds = natural logarithm of Odds Ratio

	Chi-Square		
	Phi	**Yates**	**Pearson**
	+0.07	6.76	7.16
P		0.009322	0.007455

Chi-square is calculated only if all expected cell frequencies are equal to or greater than 5. The Yates value is corrected for continuity; the Pearson value is not. Both probability estimates are non-directional.

Fisher Exact Probability Test:

P	**one-tailed**	Sample size too large
	two-tailed	for the Fisher test.

Home	Click this link **only** if you did not arrive here via the VassarStats main page.

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